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Vascular endothelial growth factor gene transfer therapy for coronary artery disease: A systematic review and meta-analysis

Rong Yuan[1,2] | Qiqi Xin[2] | Weili Shi[2] | Wei Liu[3] | Simon-M. Lee[4] | Puiman Hoi[4] | Lin Li[5] | Jun Zhao[6] | Weihong Cong[2] | Keji Chen[2]

[1]Graduate School, Beijing University of Chinese Medicine, Beijing, China

[2]Laboratory of Cardiovascular Diseases, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

[3]Cardiovascular Department, Beijing Hospital of TCM Affiliated to the Capital Medical University, Beijing, China

[4]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, China

[5]Laboratory of Neurodegenerative Diseases, Xuanwu Hospital, Capital Medical University, Beijing, China

[6]Traditional Chinese Medicine Department, The Affiliated Hospital of Qingdao University, Qingdao, China

Correspondence: Keji Chen and Weihong Cong, Laboratory of Cardiovascular Diseases 305, Xiyuan Hospital, China Academy of Chinese Medical Sciences, 1 Xiyuan Playground, Haidian District, Beijing, 100091, China (kjchenvip@163.com; congcao@188.com).

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Summary

Aim: It is not clear whether treatment by vascular endothelial growth factor (VEGF) gene transfer can improve myocardial ischemia through a proangiogenesis mechanism and is effective against coronary artery disease (CAD). We aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared VEGF gene therapy and standard treatments in CAD.

Methods: We systematically searched the PubMed, Embase, and Cochrane databases and relevant references for RCTs (published up to May 2018; no language restrictions) and performed meta-analysis using both fixed and random effects models. Our primary outcome measures were mortality and serious cardiac events. The secondary outcome measures were follow-up left ventricular ejection fraction (LVEF), change in LVEF (ΔLVEF), and angina outcomes. The registration number is CRD42017058430.

Results: Of 524 identified studies, 14 were eligible and were included in our analysis. At a mean follow-up of 6 months, VEGF gene therapy demonstrated a decreased risk of serious cardiac events (11.7% vs 21.2%, relative risk: 0.56; 95% confidence interval (CI): 0.37, 0.84; $P = 0.005$) and a slight improvement in follow-up LVEF (weighted mean difference: 1.95; 95%CI: 1.28, 2.62). Furthermore, VEGF gene therapy using adenoviral vectors showed more potential benefit in terms of the risk of serious cardiac events, ΔLVEF, and Canadian Cardiovascular Society angina class. Nevertheless, mortality and angina frequency scores were not different.

Conclusions: Vascular endothelial growth factor gene therapy appears to be safe and effective regarding serious cardiac events, with greater benefit when using adenoviral vectors. This meta-analysis highlights the need for further exploration in these areas.

KEYWORDS

angina pectoris, angiogenesis inducing agents, coronary artery disease, genetic therapy, myocardial ischemia, vascular endothelial growth factor

Yuan and Xin contributed equally to this work.

1 | INTRODUCTION

Coronary artery disease (CAD) has become the major cause of death and illness worldwide.[1] According to the World Health Organization, CAD is the leading cause of death worldwide among all noncommunicable diseases.[2] Current therapeutic options are limited to pharmacological therapy, percutaneous coronary intervention, and bypass surgery; however, a large number of patients do not qualify for surgical or interventional procedures, and many patients have refractory angina despite maximal medical therapy.[3] These limitations have led to extensive research to find new treatment modalities.

Coronary artery disease causes a lack of coronary blood flow, and all therapeutic interventions should aim to improve blood flow to the ischemic myocardium.[4] Therapeutic angiogenesis represents a novel treatment option for patients with CAD as it can increase blood flow and repair injured and dead myocardium.[5,6] The vascular endothelial growth factor (VEGF) family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor (PLGF), which are key regulators of angiogenesis and lymphangiogenesis. There are two predominant isoforms of VEGF-A, VEGF-A121, and VEGF-A165, which are the most potent stimulators of angiogenic processes. VEGF-B plays a role in the maintenance of newly formed blood vessels under pathological conditions. VEGF-C and VEGF-D are primarily lymphangiogenic factors that can also induce angiogenesis. PLGF has a particular role in inflammatory responses and pathological permeability.[7-9] Currently, VEGF-A, VEGF-C, and VEGF-D are mainly used in CAD in clinical trials.[10,11]

Gene therapy is the therapeutic delivery of nucleic acid into cells to treat disease. In VEGF gene therapy, DNA encoding VEGF is transferred into cells in the ischemic myocardium, which subsequently grows new blood vessels; such therapy is a potential new treatment option.[12,13] To date, this intriguing approach to using VEGF gene therapy for CAD has been pursued in several clinical trials, but the results have been inconsistent.[14,15] Furthermore, several studies have suggested that VEGFs can accelerate the process of atherosclerosis in certain animal models and potentially destabilize coronary plaques.[16,17] These findings contradict the effect of angiogenesis therapy on CAD, as most patients with CAD suffer from atherosclerosis. Hence, this therapy remains controversial, and there is no related meta-analysis. Therefore, we aimed to perform a systematic review and meta-analysis of the role of VEGF gene therapy for CAD.

2 | METHODS

2.1 | Search strategy

This systematic review and meta-analysis are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Additionally, we registered the current meta-analysis at the international prospective register of systematic reviews (number: CRD42017058430).[18]

We selected randomized controlled trials (RCTs) containing VEGF gene therapy published up to May 2018 by searching the PubMed, Embase, and Cochrane databases and relevant references. Medical search terms included the following: "vascular endothelial growth factor gene" OR "VEGF gene" AND "coronary artery disease" OR "CAD" OR "coronary heart disease" OR "CHD" OR "angina" AND "randomized controlled trial." We also performed a manual search. Two investigators (RY and QX) independently performed the database search and study selection.

2.2 | Inclusion and exclusion criteria

We considered studies for inclusion if they met all of the following criteria: (a) RCTs comparing VEGF gene therapy and standard treatments for CAD; (b) report of at least one of the outcomes of interest (mortality, serious cardiac events, follow-up left ventricular ejection fraction (LVEF), change in LVEF (ΔLVEF), and angina). Studies were excluded for the following reasons: VEGF treatment not involving gene therapy (such as VEGF protein treatment), nonrandomized study design, duplicate publication, unpublished abstracts, or no reported outcomes of interest.

2.3 | Data extraction and management

Two independent investigators (RY and QX) reviewed the study and extracted the data. Any further calculations on study data were conducted by the first reviewer and checked by the second reviewer. Disagreements were resolved by consensus. Descriptive data extracted included the first author's name, year of publication, study design, total sample size, type of CAD, VEGF gene type, control treatment type, outcomes, and adverse effects. The primary outcomes were mortality and serious cardiac events. Serious cardiac events included myocardial infarction, acute coronary syndrome, cardiac arrest, cardiogenic shock, heart failure, and surgical cardiac interventions. The secondary outcome measures were follow-up LVEF, ΔLVEF, Canadian Cardiovascular Society (CCS) angina class, and angina frequency scores in the Seattle Angina Questionnaire.

2.4 | Quality assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to assess the methodological quality of the included studies. The seven items in this tool address the adequacy of randomization and allocation concealment, blinding, completeness of outcome data, selective reporting, and other bias.

2.5 | Statistical analysis

The relative risk (RR) and 95% confidence interval (CI) were calculated to assess differences in mortality and serious cardiac events. The data represent the weighted mean difference (WMD) and 95% CI of LVEF, CCS angina class, and angina frequency scores. We conducted subgroup analysis according to CAD type, VEGF gene

type and delivery method, and performed sensitivity analyses. We assessed publication bias by constructing a funnel plot and using Begg's and Egger's tests. A formal assessment of statistical heterogeneity was made using the I^2 statistic. A fixed effects model was used when $I^2 < 50\%$, and a random effects model was used when $I^2 > 50\%$. Analyses were performed with Review Manager 5.3 and Stata 12.0 software.

3 | RESULTS

3.1 | Description of included studies

A total of 524 studies were identified, and 124 records were removed because they were duplicates. By screening titles and abstracts, we excluded 375 records because they were experimental studies, review articles, non-CAD studies, or non-VEGF gene therapy studies. By browsing full-text articles, we excluded 11 records for not being RCTs, not involving VEGF gene therapy, or having no outcome information. Finally, a total of 14 RCTs were included.[13-15,19-29] Only one trial reported outcomes at 8 years (Hedman et al[29]), and this publication reported the same patients as Hedman et al. 2003; the other trials reported outcomes at less than 1 year. A flowchart of the study selection was generated according to the PRISMA requirements (Figure 1).

3.2 | Risk of bias assessment

All the included studies were RCTs. Six trials reported the method of double-blinding,[14,15,24,26,27,29] 8 studies reported allocation concealment,[14,15,20,23,24,26,27,29] 7 trials reported complete outcome data,[14,15,19-21,24,29] and three trials may have had selective reporting.[22,25,27] There was an unclear risk of bias in allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. There was a high risk of bias in blinding (Figure 2).

3.3 | Study characteristics

In this meta-analysis, 1 of the 13 articles contained two studies, and Hedman et al[26] presented the results of patients exposed to plasmid or adenovirus vector separately in one article. All the clinical studies were published in English from 2001 to 2017. A final total of 550 patients

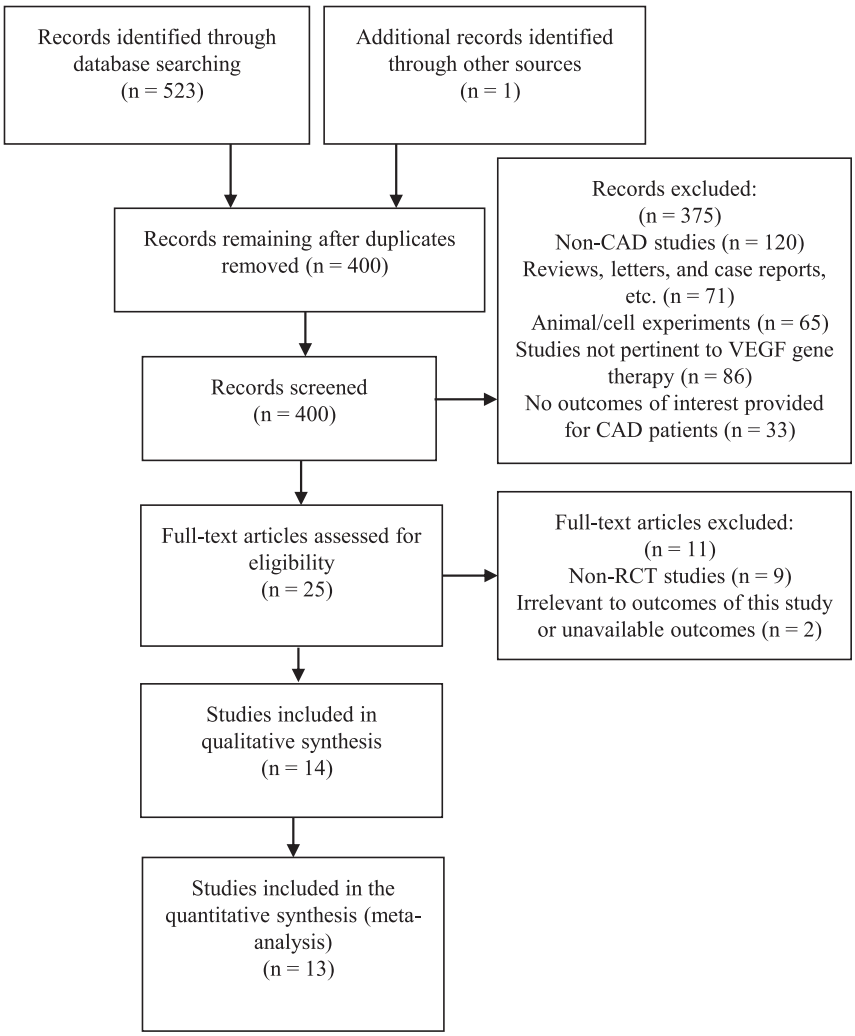

FIGURE 1 Search strategy and study inclusion criteria. CAD, coronary artery disease; RCT, randomized controlled trials; VEGF, vascular endothelial growth factor

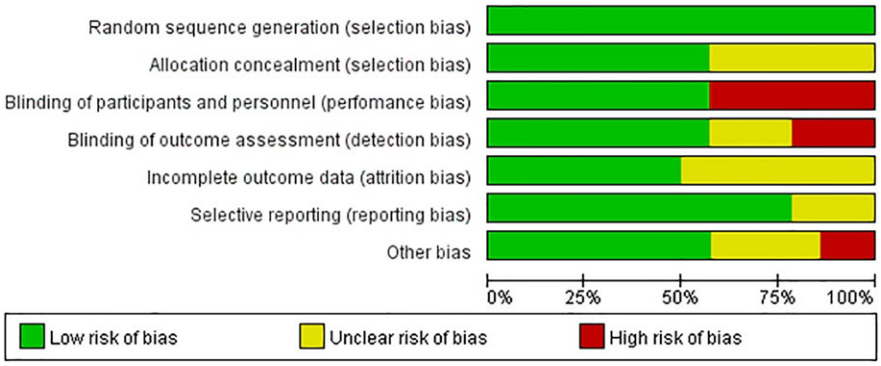

FIGURE 2 Diagram showing risk of bias in the included studies

(234 patients in the control group and 316 patients in the VEGF gene therapy group) were included. Subject age ranged from 56 to 71 years. The mean trial duration was 6 months (range: 3-12 months). Table 1 shows the distribution of these studies according to study design, patient characteristics, treatment measures, and adverse effects.

3.4 | Primary outcome

The outcome measures were not reported in all of the trials. In this meta-analysis, seven studies assessed mortality.[13,14,19-22,24] There was no statistically significant difference in mortality between the VEGF gene therapy group and the control group (RR: 0.79; 95%CI: 0.29, 2.13; $P = 0.64$), although the subgroup analysis was performed on different VEGF gene types and vectors. We detected no significant heterogeneity (Figure 3A). The overall sample size was relatively small, and publication bias cannot be evaluated for mortality. In addition, Hedman et al[29] presented the mortality at 8 years of patients grouped by vector type in one article. VEGF gene therapy with an adenovirus vector tended to decrease the risk of mortality (RR: 0.75: 95%CI: 0.14, 4.05), while VEGF gene therapy with a plasmid vector did not decrease the risk of mortality (RR: 1.15: 95%CI: 0.11, 11.68) at 8 years.

In this meta-analysis, 10 studies assessed serious cardiac events.[13-15,19-22,24,26] Pooling data from these studies showed that VEGF gene therapy led to a significantly decreased risk of serious cardiac events (11.7% vs 21.2%, RR: 0.56; 95%CI: 0.37, 0.84; $P = 0.005$). In the subgroup analysis, the risk of serious cardiac events was significantly lower in the VEGF-A165 gene therapy group (RR: 0.52; 95%CI: 0.30, 0.91) and in the adenovirus vector group (RR: 0.55; 95%CI: 0.31, 0.96). We detected no significant heterogeneity (Figure 3B). In this analysis, there was no significant publication bias ($P = 0.94$), and the funnel plot is shown in Figure 3C. In addition, Hedman et al[29] presented serious cardiac events over 8 years in patients grouped by vector type in one article; VEGFgene therapy with an adenovirus vector (RR: 0.71; 95%CI: 0.34, 1.52) or a plasmid vector (RR: 0.79; 95%CI: 0.41, 1.52) tended to decrease the risk of serious cardiac events at 8 years.

3.5 | Secondary outcomes

In this meta-analysis, seven studies (N = 219 participants) assessed LVEF.[14,15,22-24,27,28] Follow-up LVEF improved in the VEGF gene therapy group (WMD: 1.95; 95%CI: 1.28, 2.62; $P < 0.00001$). In the subgroup analysis, follow-up LVEF improved in the VEGF-A165 gene therapy group (WMD: 2.03; 95%CI: 1.36, 2.70) and the plasmid vector group (WMD: 2.00; 95%CI: 1.33, 2.68). There was no statistically significant heterogeneity (Figure 4A). Then, we performed an analysis of ΔLVEF, and the overall effect on ΔLVEF was not significantly different between the two groups. In the subgroup analysis, ΔLVEF significantly increased in the VEGF-A121 gene therapy group and the adenovirus vector group (WMD: 4.74; 95%CI: 2.76, 6.71) (Figure 4B). Publication bias could not be evaluated because of the relatively small sample size.

In this meta-analysis, seven studies assessed CCS angina class during a mean period of 6 months.[14,15,20,21,24,26] There is no significant benefit of VEGF gene therapy on CCS angina class. In the subgroup analysis, the CCS angina class was significantly lower in the adenovirus vector group (WMD: −0.92; 95%CI: −0.99, −0.86), while the opposite effect was observed in the plasmid vector group (WMD: 0.33; 95%CI: 0.27, 0.40). There was no significant difference based on VEGF gene type or CAD type (Figure 4C).

In this meta-analysis, 4 studies assessed the angina frequency scores in the Seattle Angina Questionnaire.[21,23,24,27] Pooling the data revealed no significant benefit of VEGF gene therapy (WMD: 11.97; 95%CI: −1.29, 25.23, $P = 0.08$). In the subgroup analysis, patients treated with VEGF-A165 showed an increased angina frequency score in only one trial (Kastrup et al[24]) (WMD: 5.00; 95%CI: 3.02, 6.98). VEGF-C treatment also evoked an increased angina frequency score in only one trial (Losordo et al[27]) (WMD: 18.00; 95%CI: 14.40, 21.60), and VEGF-A121 had no effect on angina frequency scores (Figure 4D).

3.6 | Sensitivity analyses

In sensitivity analyses, the pooled effect estimates showed no significant differences in follow-up LVEF upon excluding the study by Kastrup et al,[24] which indicated that this result was not robust. Individual study exclusion did not substantially change the pooled effect estimate of other outcomes.

3.7 | Adverse effects

Five trials described the adverse effects in detail,[13,15,19,20,26] and the remaining trials reported no adverse effects. The main adverse effects were peripheral vascular disorder, peripheral edema, retinal

TABLE 1 Characteristics of randomized controlled trials of VEGF gene transfer therapy in coronary artery disease (sort by year of publication)

Study (design)	Number (T/C)	Age	Number of man(T/C)	VEGF gene treatment type	Type of CAD	Time	Control treatment	Outcomes of interest	Adverse effects
Hartikainen, J. 2017[13]	30 (24/6)	71/70	23/5	0.2 mL Ad-VEGF-D	Refractory CAD	3, 12 mo	Placebo injection	Safe, feasible, well tolerated, increased myocardial perfusion	Minor bleeding, new atrial fibrillation, pericardial effusion
Muona, K. 2013[19]	15 (12/3)	71/68	12/3	1 x 10^{10} particle units (p.u.) Ad-VEGF-D	Severe CAD	3 mo	Placebo injection	Safe, feasible, well tolerated	Pyelonephritis, pericardial effusion, significant elevation in prostate-specific antigen, inflammation and immunological findings
Kukula, K. 2011[14]	52 (33/19)	62.8/61.7	24/16	0.5 mg PL-VEGF-A165	Refractory CAD	5, 12 mo	Placebo plasmid	Safe but did not improve myocardial perfusion, while improve symptoms	No adverse events
Kastrup, J. 2011[15]	17 (12/5)	60.9/64.1	9/4	4 x 10^{10} p.u. Ad-VEGF-A121	Refractory CAD	12, 26 wk, 12 mo	Placebo infusion	Safe but did not improve myocardial perfusion	Vertigo, abdominal pain, influenza/rhinitis, conjunctivitis, pneumonia, hypertension, syncope, back pain, liver function abnormality, peripheral vascular disorder
Hedman, M.2009a[29]	48 (32/16)	58/56	26/15	2 x 10^{10} p.u. Ad-VEGF-A165	Refractory CAD	8 y	Placebo infusion	Safe and does not increase the risk of major adverse cardiovascular events, arrhythmias, cancer, diabetes	Not reported
Hedman, M.2009b[29]	41 (26/15)	58/56	23/15	0.2 mg PL-VEGF-A165					
Stewart, D.J. 2009[20]	93 (48/45)	63/64	40/42	2 mg PL-VEGF-A165	Refractory CAD	3, 6 mo	Placebo infusion	No benefit on any of the endpoints	Musculoskeletal pains, headache, cancer dizziness, pericardial, gastrointestinal, dermatological, retinal, peripheral edema, neurological, inflammation, hypotension
Stewart, D.J. 2006[21]	67 (32/35)	61/60	26/32	4 x 10^{10} p.u. Ad-VEGF-A121	Refractory CAD	12, 26 wk	Medication	No difference in adverse events	No adverse events
Ripa, R.S. 2006[22]	32 (16/16)	61/62	15/14	0.5 mg PL-VEGF-A165	Refractory CAD	3 mo	Placebo infusion	Safe but did not improve myocardial perfusion or clinical effects	No adverse events

(*Continues*)

TABLE 1 (Continued)

Study (design)	Number (T/C)	Age	Number of man(T/C)	VEGF gene treatment type	Type of CAD	Time	Control treatment	Outcomes of interest	Adverse effects
Fuchs, S.2006[23]	10 (6/4)	61/69	61/69	4 x 10^{10} p.u. Ad-VEGF-A121	Refractory CAD	3 mo, 12 mo	Placebo infusion	Practical, feasible, and potentially safe	No significant changes
Kastrup, J.2005[24]	80 (40/40)	61/61	33/35	0.5 mg PL-VEGF-A165	Severe CAD	3 mo, follow-up 6 mo	Placebo plasmid	Safe but did not improve myocardial perfusion	No serious adverse events
Tio, R. A. 2004[25]	23 (10/13)	63/64	9/9	0.5 mg PL-VEGF-A165	End-stage CAD	3 mo	Medication	Decreased myocardial ischemia	Not reported
Hedman, M.2003[a 26]	56 (37/19)	58/56	26/15	2 x 10^{10} p.u. Ad-VEGF-A165	Stenosis, suitable for stenting	6 mo, follow-up 28 mo	Placebo infusion	Safe and increase myocardial perfusion	Transient fever, transient elevation of serum C-reactive protein, palindromic joint symptoms, colitis, and other gastrointestinal symptoms
Hedman, M.2003[b 26]	47 (28/19)	58/56	23/15	0.2 mg PL-VEGF-A165					
Losordo, D.W.2002[27]	19 (12/7)	62/59	9/6	0.2 mg PL-VEGF-C	Refractory CAD	12 wk	Placebo plasmid	Safe and reduce angina class	No major complications
Vale, P. R.2001[28]	9 (6/3)	67/67	5/5	0.2 mg PL-VEGF-C	Refractory CAD	3,12 mo	Placebo plasmid	Feasibility, safety, and improve left ventricular myocardium	No major complications

Ad, adenovirus; CAD, coronary artery disease; p.u., particle units; PL, plasmid; T/C, treatment/control; VEGF, vascular endothelial growth factor.

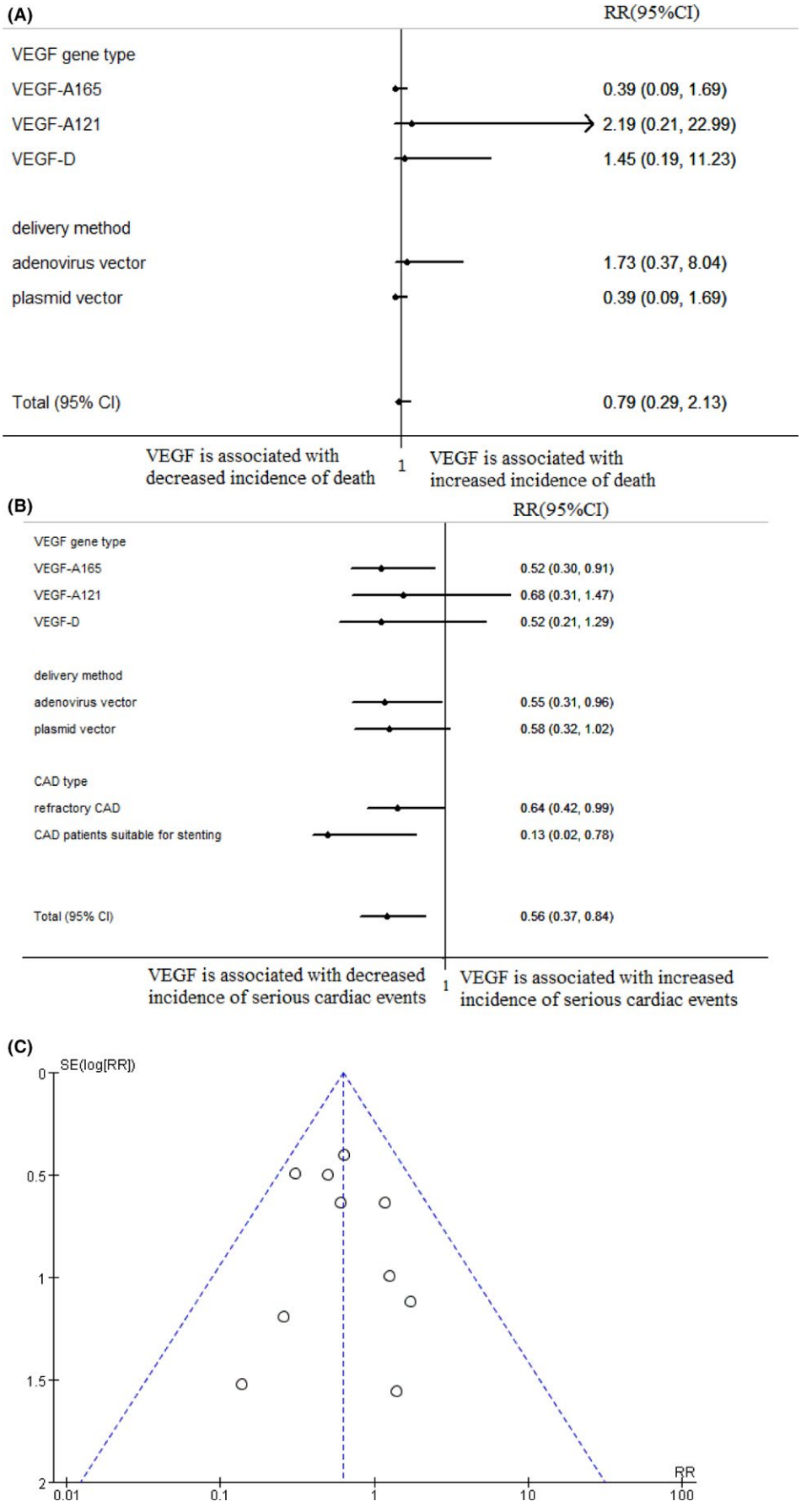

FIGURE 3 Meta-analyses of VEGF gene therapy for CAD, comparing mortality and serious cardiac events. Outcomes assessed are (A) mortality, (B) serious cardiac events. (C) Funnel plot of serious cardiac events. CI, confidence interval; CAD, coronary artery disease; VEGF, vascular endothelial growth factor

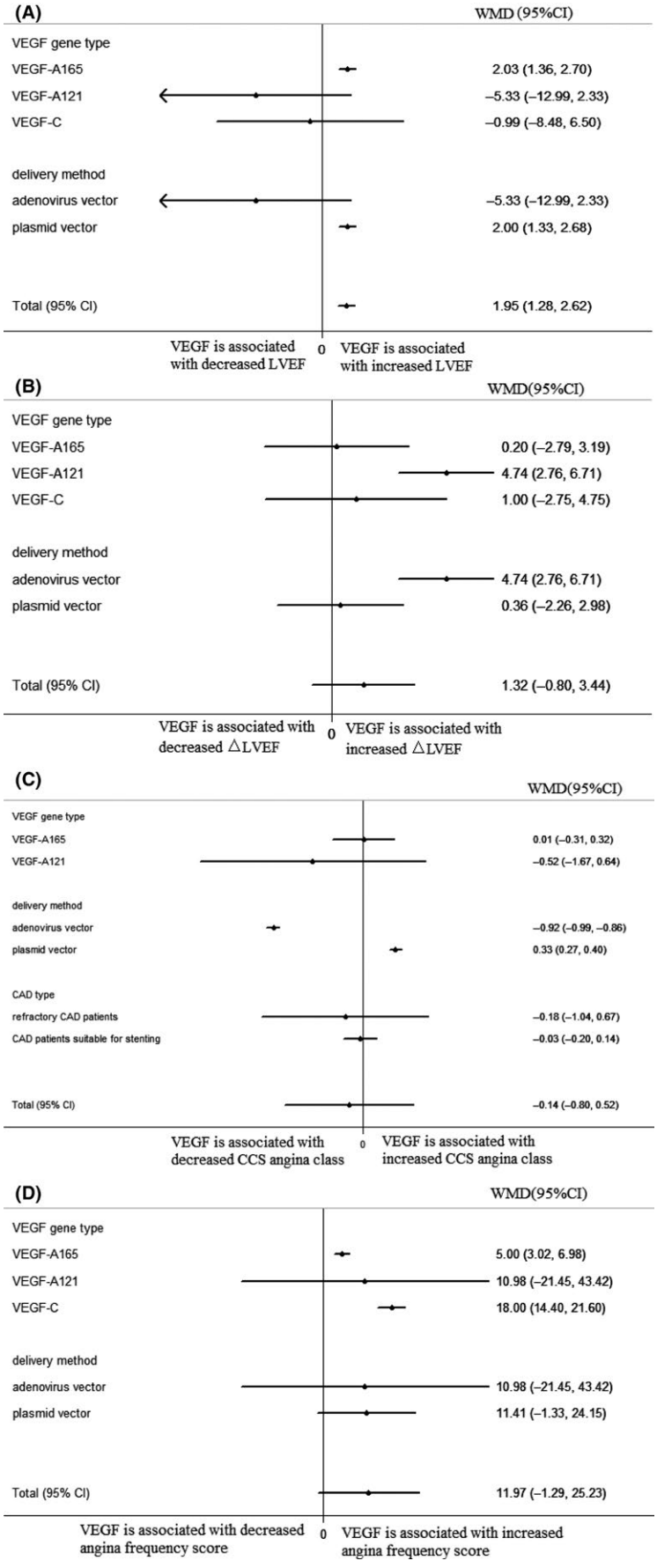

FIGURE 4 Meta-analyses of VEGF gene therapy for CAD, comparing LVEF, △LVEF, CCS angina class, and angina frequency score. Outcomes assessed are (A) LVEF, (B)△LVEF, (C) CCS angina class, and (D) angina frequency score. CI, confidence interval; CAD, coronary artery disease; VEGF, vascular endothelial growth factor; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society

disease, musculoskeletal pain, inflammation, and pericardial effusion. Most of the adverse effects showed no difference between the two groups, except in two studies: musculoskeletal pain in the study by Stewart et al[20] and transient fever and transient elevation of serum C-reactive protein in the study by Hedman et al[26]

4 | DISCUSSION

Our results showed that VEGF gene therapy could decrease the risk of serious cardiac events and slightly improve follow-up LVEF, which reflects the hopeful prospects for the treatment of CAD. In addition, VEGF gene therapy had no effect on the risk of mortality. The neutral results suggest that VEGF gene therapy for CAD is safe, but studies with longer follow-up and larger sample sizes are needed to confirm this result. Furthermore, VEGF gene therapy did not improve the angina frequency score. In the subgroup analysis, VEGF gene delivery using adenoviral vectors improved the risk of serious cardiac events, ΔLVEF, and CCS angina class, while the evidence for plasmid vectors was not sufficient. Moreover, VEGF-A165 may decrease the risk of serious cardiac events, and VEGF-A121 may increase ΔLVEF compared with other VEGF gene types. In addition, heterogeneity could not be fully investigated because of the small sample size, and the results require further validation. Overall, these data support the hypothesis that VEGF gene transfer, especially using adenoviral vectors, is a safe potential therapy for CAD that is beneficial in terms of serious cardiac events, albeit with no effect on mortality or angina frequency scores. Therefore, this meta-analysis highlights the need for further exploration in these areas.

Improving blood flow to the ischemic myocardium plays a critical role in the treatment of CAD.[4] VEGF-A165 and VEGF-A121 both induce angiogenesis and increase blood flow. VEGF-A165 is more highly expressed than VEGF-A121, while VEGF-A121 diffuses more into the ischemic milieu than VEGF-A165; VEGF-C and VEGF-D stimulate lymphatic vessel growth and do not directly stimulate inflammatory responses.[8,13,30-32] This meta-analysis showed that VEGF-A165 gene transfer could decrease the risk of serious cardiac events and that VEGF-A121 gene transfer could increase ΔLVEF, which indicated that VEGF-A165 may have greater potential in the prognosis of CAD, and VEGF-A121 may be more beneficial in improving cardiac function; while these results should be further investigated. Furthermore, there have been only two studies on VEGF-C (Losordo et al[27]; Vale et al[28]) and VEGF-D (Hartikainen et al[13]; Muona et al[19]), and there is no evidence of improvement; however, these issues must be further explored.

This meta-analysis showed robust and consistent findings that lend support to the safety and efficacy of VEGF gene therapy in reducing the risk of serious cardiac events while not affecting mortality. Indeed, these results were consistent across studies despite several differences, including in VEGF type, CAD type, gene delivery method, and control treatment. Taken together, the results of these studies support the beneficial effects of VEGF gene therapy across clinical settings.

The results showed that VEGF gene therapy could slightly improve follow-up LVEF but not ΔLVEF, which is unlikely to be clinically important. Follow-up LVEF appeared to improve in the VEGF-A165 gene therapy group and the plasmid vector group, but these results were dominated by one study (Kastrup et al[24]) and thus not robust. In addition, findings remain controversial with respect to the effectiveness of VEGF gene therapy in improving angina. The CCS angina class was decreased by VEGF gene delivery using adenoviral vectors but increased by plasmid vectors, which may indicate that these two vector types have different effects on angina. In addition, although it seemed that VEGF-A165 and VEGF-C increased angina frequency scores, there was only one trial in each group, and more studies are needed. Regarding the high heterogeneity, CAD type, VEGF gene type, delivery method, and treatment duration were taken into account; however, the heterogeneity was not eliminated, so these results should be interpreted cautiously.

Genes encoding VEGFs can be transfected into the myocardium by plasmid DNA or adenovirus vectors.[7,33,34] Recently, the use of adenovirus has gained popularity due to higher cardiac tropism and promising preclinical results.[34] Our results also showed that gene delivery using adenoviral vectors prompted improvements in serious cardiac events, ΔLVEF, and CCS angina class, which indicated that more efficient adenovirus transfection could be necessary to induce neovascularization in the ischemic myocardium.

In this meta-analysis, most of the trials reported no adverse effects, while two trials showed a significant difference in musculoskeletal pain, transient fever, and transient elevation of serum C-reactive protein between the two groups,[20,26] which may be correlated with adverse effects of the VEGF-A gene.[35] Moreover, adenovirus vectors may increase the risk of inflammatory activation, while most of these adverse effects alleviated after discontinuing treatment. However, more attention still should be paid to the use of VEGF gene transfer for angiogenic diseases, such as atherosclerotic disease, rheumatoid disease, retinal disease, and malignant tumors.[29,36,37]

Our meta-analysis has several limitations. First, differences in study design are likely to have introduced heterogeneity in ΔLVEF, CCS angina class, and angina frequency scores. Although we performed subgroup analyses, difference remained among the studies in terms of the sample size, race, religious beliefs, and concern regarding the disease. Second, most of the included studies had a relatively small sample size and might be methodologically less robust, potentially leading to overestimation of treatment effects. Third, the long-term persistence of the treatment effects is unknown. Most of the trials ranged in duration from 3 to 12 months, and only one trial reported long-term follow-up.[29] Fourth, the publication bias could not be evaluated in all outcomes because of small sample size. In the bias evaluation, we emailed all the corresponding authors, but unfortunately, only one author replied in detail. Finally, the ideal time to begin this treatment in the clinical course of the disease is unknown. The outcomes and conclusions should be interpreted with these limitations in mind.

Therapeutic angiogenesis is still a promising new treatment for patients with CAD. However, more research, including large-scale, double-blind, randomized, placebo-controlled, multicenter trials with a standardized design, is needed to validate and verify the efficacy of VEGF gene therapy as a reliable supportive therapeutic option in CAD.

5 | CONCLUSION

VEGF gene therapy appears to be associated with a reduction in serious cardiac events and a slight improvement in follow-up LVEF, and adenoviral vectors seem to have more benefit in terms of the risk of serious cardiac events, ΔLVEF, and CCS angina class and thus may be useful in proangiogenesis regimens for patients with CAD. However, further clinical trials are needed to establish the optimal approach for the application of this treatment in practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

RY, QX, WC, and KC had the idea for the study. RY and QX selected studies for inclusion and abstracted data. RY, QX, WS, and WL analyzed the data. All authors interpreted the data and wrote the manuscript. All authors approved draft.

ORCID


Rong Yuan http://orcid.org/0000-0002-6824-3055

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