Table 2 Myocardial vascularization clinical trials using recombinant proteins

Protein	Route	Trial	n	Primary Endpoint	Outcomes	Clinical Trial Identifier	Reference
FGF-1	IM	Phase I	20	Neoangiogenesis in angiography at 90 days	Increased capillary density, but no evidence of improved coronary perfusion or ventricular function		[73]
FGF-2	IC	Phase I	25	Safety monitoring and tolerability at 3 days	Dose-escalation trial; doses of 3 to 30 μg/kg was generally well tolerated in subjects with stable angina; no signs of systemic angiogenesis		[74]
	IC	Phase I	52	ETT at 29 days	Improvements in exercise tolerance and reduction in size of ischemic area		[75]
	IC/IV	Phase I	59	Improved myocardial perfusion at 29 days	Ascending dose trial; improvement in perfusion and attenuation of stress-induced ischemia; no control group		[92]
	IC	Phase II	337	ETT and angina frequency at 90 days	FIRST study; significant reduction in symptoms of angina at 90 days follow-up, but no longer detectable at 180 days; no improvement in ETT time and myocardial perfusion		[76]
VEGF-A	IC	Phase I	14	Improved myocardial perfusion at 30 days	Some improvement in perfusion in patients treated with low-dose rhVEGF-A; five of six patients had perfusion improvement on rest and stress at higher doses		[78]
	IC	Phase I	15	Improved myocardial perfusion at 60 days	Dose screening study; well tolerated up to 0.05 mg/kg/min; myocardial perfusion imaging was improved in 7 of 14 patients at 60 days		[79]
	IV	Phase I	28	Myocardial perfusion	Evidences of improvement in rest myocardial perfusion and in collateral density		[77]
	IC/IV	Phase II	178	ETT at 60 days	VIVA study; safe and well tolerated; no improvement beyond placebo in all measurements by day 60. By day 120, high-dose rhVEGF-A resulted in significant improvement in angina; no improvements in exercise tolerance; no improvements in myocardial perfusion		[80]
G-CSF	SC	Phase I	52	Coronary collateral flow and ECG at 14 days	Subcutaneous G-CSF is efficacious during a short-term protocol in improving signs of myocardial salvage by coronary collateral growth promotion	ClinicalTrials.gov NCT00596479	[81]
	SC	Phase II	60	LVEF at 180 days	Increased end-diastolic volume from baseline to 6 months in the placebo group but unchanged in the G-CSF group; no significant differences in LVEF or perfusion between groups		[82]
	SC	Phase III	100	Adverse events and compliance at 6 weeks	SITAGRAMI-Trial; combined application of G-CSF and Sitagliptin; planned first interim-analysis on safety issues: only two major adverse cardiac events occurred (one de novo stenosis and one in-stent-restenosis) in the first 36 patients	EudraCT Number 2007-003941-34	[84]
NRG	IV	Phase I	15	Haemodynamics at 2h and LVEF at 12 weeks	Acute and sustained improvements in cardiac function; safe and well tolerated; no control group	ACTRN12607000330448	[51]
	IV	Phase II	44	LV function and structure at 90 days	Progressive improvement of cardiac function and anti remodeling effect in patients with chronic heart failure, but no statistically significant differences	ChiCTR-TRC-00000414	[52]

EPO	IV	Phase I	44	Erythropoietin activity; angiogenesis markers	Evidence of safety and biologic activity of erythropoietin in patients with acute myocardial infarction; increased expression of angiogenesis signaling proteins	ClinicalTrials.gov NCT00367991	[86]
	IV	Phase II	529	LVEF at 6 weeks	A single high dose of EPO did not improve LVEF after 6 weeks	ClinicalTrials.gov NCT00449488	[87]

FGF-1: acidic Fibroblast Growth Factor; FGF-2: basic Fibroblast Growth Factor; VEGF: Vascular Endothelial Growth Factor; G-CSF: Granulocyte colony-stimulating factor; NRG: Neuregulin; EPO: Erythropoietin; IM: Intramyocardial; IC: Intracoronary; IV: Intravenous; SC: Subcutaneous; LVEF: Left ventricle ejection fraction; ETT: exercise tolerance testing; ECG: electrocardiogram; ANZCTR: Australian New Zealand Clinical Trials Registry, http://www.anzctr.org.au; ChiCTR: Chinese Clinical Trial Registry, http://www.chictr.org/; EudraCT: European Clinical Trials Database, https://eudract.ema.europa.eu/.