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Clinical Investigation

Randomized placebo controlled trial evaluating the safety and efficacy of single low-dose intracoronary insulin-like growth factor following percutaneous coronary intervention in acute myocardial infarction (RESUS-AMI)

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ABSTRACT

Background: Residual and significant postinfarction left ventricular (LV) dysfunction, despite technically successful percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI), remains an important clinical issue. In preclinical models, low-dose insulin-like growth factor 1 (IGF1) has potent cytoprotective and positive cardiac remodeling effects. We studied the safety and efficacy of immediate post-PCI low-dose intracoronary IGF1 infusion in STEMI patients.

Methods: Using a double-blind, placebo-controlled, multidose study design, we randomized 47 STEMI patients with significantly reduced (≤40%) LV ejection fraction (LVEF) after successful PCI to single intracoronary infusion of placebo (n = 15), 1.5 ng IGF1 (n = 16), or 15 ng IGF1 (n = 16). All received optimal medical therapy. Safety end points were freedom from hypoglycemia, hypotension, or significant arrhythmias within 1 hour of therapy. The primary efficacy end point was LVEF, and secondary end points were LV volumes, mass, stroke volume, and infarct size at 2-month follow-up, all assessed by magnetic resonance imaging. Treatment effects were estimated by analysis of covariance adjusted for baseline (24 hours) outcome.

Results: No significant differences in safety end points occurred between treatment groups out to 30 days (χ^2 test, P value = .77). There were no statistically significant differences in baseline (24 hours post STEMI) clinical characteristics or LVEF among groups. LVEF at 2 months, compared to baseline, increased in all groups, with no statistically significant differences related to treatment assignment. However, compared with placebo or 1.5 ng IGF1, treatment with 15 ng IGF1 was associated with a significant improvement in indexed LV end-diastolic volume ($P = .018$), LV mass ($P = .004$), and stroke volume ($P = .016$). Late gadolinium enhancement (±SD) at 2 months was lower in 15 ng IGF1 (34.5 ± 29.6 g) compared to placebo (49.1 ± 19.3 g) or 1.5 ng IGF1 (47.4 ± 22.4 g) treated patients, although the result was not statistically significant ($P = .095$).

Conclusions: In this pilot trial, low-dose IGF1, given after optimal mechanical reperfusion in STEMI, is safe but does not improve LVEF. However, there is a signal for a dose-dependent benefit on post-MI remodeling that may warrant further study.

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Conflict of interest: N. M. Caplice is a named inventor on intellectual property owned by University College Cork relating to cardiac repair post myocardial infarction.

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Despite timely reperfusion by primary percutaneous coronary intervention (PPCI), a significant cohort of patients develops adverse left ventricular remodeling with clinical sequelae such as arrhythmia and heart failure.[1] Therapeutic approaches to avert such remodeling, including a variety of cell therapy and ischemia-reperfusion injury mitigation trials, have achieved modest success.[2,3] Thus, there remains a significant opportunity for novel therapies in this field.

Conceptually, one approach to aid remodeling post large myocardial infarction (MI) would be to target early cardiomyocyte death, reducing subsequent inflammation, loss of myocardial mass, and fibrous scar formation post-STEMI. Insulin-like growth factor 1 (IGF1) is a potential candidate for such a role: it is essential for constitutive cardiomyocyte function and survival[4]; has high receptor expression in at-risk cardiomyocytes postinfarction[5]; and acts both as a potent inhibitor of cell death and a stimulant of resident stem cell mobilization, tissue repair, and cardiac remodeling postinfarction when administered exogenously by diverse delivery approaches.[6-10] However, IGF1 therapy has never been used in humans post-MI predominantly due to previous negative experience with high-dose studies of human growth hormone (hGH) in heart failure trials in the mid-1990s.[11-14] Because of unproven efficacy and adverse effects experienced with hGH (which acts via IGF1 in vivo),[14] it was presumed that IGF1 would present similar challenges to use in humans, and given the presence of several IGF binding peptides in the circulation, it was also expected that exogenous IGF1 would have reduced bioavailability when administered intravenously.[8]

However, IGF1, a small protein, may be ideal for intracoronary delivery into the infarct-related artery as it exits the permeable coronary microvasculature downstream postdelivery and can act on at-risk cardiomyocytes within 30 minutes of administration as shown by previous receptor-specific signaling in preclinical studies.[5] In this work, single low-dose IGF1 given exogenously early after reperfusion post-MI induced specific activation of the cognate IGF1 receptor and downstream activation of prosurvival signaling in at-risk cardiomyocytes, leading to preservation of LV wall function and marked improvement in LV remodeling in the months posttherapy.[5]

Our aim in the current study was to examine the safety and initial efficacy across 2 low doses (a log-fold apart) of IGF1, compared to placebo, with respect to LV function and structural remodeling postinfarction in the setting of PPCI for STEMI.

Methods

Patient selection

Between November 2011 and July 2016, we performed a randomized, double-blind, placebo-controlled multidose study of LD-IGF1 in STEMI patients who had undergone successful PPCI. All patients were treated at a single site (Cork University Hospital). We included STEMI (>2 mm ST elevation in 2 contiguous leads) patients, aged between 18 and 75 years, with significant LV dysfunction at angiography left ventricular ejection fraction (LVEF≤40%). To ensure exclusion of aborted infarcts, we excluded patients presenting within 2 hours of symptoms and included those up to 12 hours of symptoms. The rationale for studying subjects up to 12 hours of symptoms related to preclinical data supporting cytoprotective effects of IGF1 on border-infract zone myocardium up to 12 hours post artery occlusion. We excluded all those patients with a previous history of structural heart disease, LV dysfunction, MI, coronary artery bypass graft, or PCI in addition to all major comorbidities including significant prior renal and hepatic dysfunction (detailed exclusion criteria are outlined in Supplementary Figure 1). Prespecified safety and efficacy end points are included in Supplementary Figure 2.

The trial was approved by the Clinical Research Ethics Committee at Cork University Hospital and the Irish Medicines Board (since renamed the Health Products Regulatory Authority), and written informed consent was obtained from all patients. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. This trial was registered on clinical trials.gov NCT01438086 and was funded by the Health Research Board of Ireland HRB TRA/2010/20.

Study design and procedures

The design of the study is shown in Figure 1. Patients were randomly assigned (with stratification for diabetes)[15] to each treatment group in a 1:1:1 ratio using sequentially numbered sealed envelopes prepared by a statistician independent of the study. We used a block size of 9 for the first 18 subjects in each stratum and a 3-subject block size thereafter. LV angiography was done just after PCI. LVEF was assessed using a validated automated QVA system (Philips, the Netherlands) to determine LVEF as ≤40%. Following successful PPCI and with Thrombolysis in Myocardial Infarction (TIMI) 3 flow in the infarct-related artery placebo containing 0.9% sodium chloride, 1.5 ng IGF1 (mecasermin; Increlex) and 15 ng IGF1 each diluted in 0.9% sodium chloride were prepared in 3-mL syringes. The method for reconstituting selected doses of IGF1 and placebo and the maintenance of double blinding and randomization to the point of administration down the coronary artery are outlined in the supplementary methods section. Therapy was delivered via a perfusion catheter (Progreat, Terumo) with the catheter tip placed at the distal end of the stent used to treat the culprit lesion, and 3 mL of the assigned solution was injected slowly over 2 minutes. Coronary angiography was performed postinjection to ensure artery patency.

Magnetic resonance imaging analysis

We performed cardiac magnetic resonance imaging (MRI) (1.5 T; Siemens) at 24 hours (range 18-36 hours) and 8 weeks post-MI. All scans were performed using commercially available MRI software, cardiac dedicated surface coils, and electrocardiographic triggering. Global and regional LV function was assessed on breath-hold cine MRI in cardiac short, vertical and long axis. *Infarct area* was defined as a zone of bright signal on late enhanced images (approximately 10 min after 10-15 mL intravenous bolus injection of gadolinium contrast) using inversion recovery gradient echo technique.

MRI data sets were analyzed on an off-line workstation (CAAS MRV 4.1; Pie Medical Imaging BV, the Netherlands) by an independent MRI core laboratory (Cardialysis BV, the Netherlands) unaware of treatment allocation. For assessment of global and regional LV function and calculation of LV mass, endocardial and epicardial borders were traced in end-diastolic and end-systolic short-axis slices. Papillary muscles were excluded from all analyses. The long-axis correction method using the 2-chamber and 4-charmber view was applied,[6] and LV end-diastolic and end-systolic volumes (LVEDV and LVESV) were calculated. *Infarct areas* were defined as hyperintense signals on late-enhanced images with inversion-recovery gradient-echo sequences. The full-width-half-maximum method was used, and further correction with a slider and manual corrections were allowed. Microvascular obstruction was included in the infarct area.

Statistical analysis

Statistical analysis was performed blinded to treatment assignment by staff at the statistical department of Cork University Clinical Research Facility. The sample size of 15 patients in each arm was based on an expected improvement in global LVEF (GLVEF) of 8 percentage points in the patients treated with 1.5 ng LD-IGF-1 (based on preclinical large-animal data generated by our group)[5] versus a 2.2–percentage point increase in the placebo arm,[16] with a shared SD of 5 percentage points. Under these assumptions and α of .05, we would detect the anticipated difference between the placebo and 1.5 ng LD-IGF-1 arms (15:15) with a power of 0.84, whereas the power would be 0.94 if comparing placebo

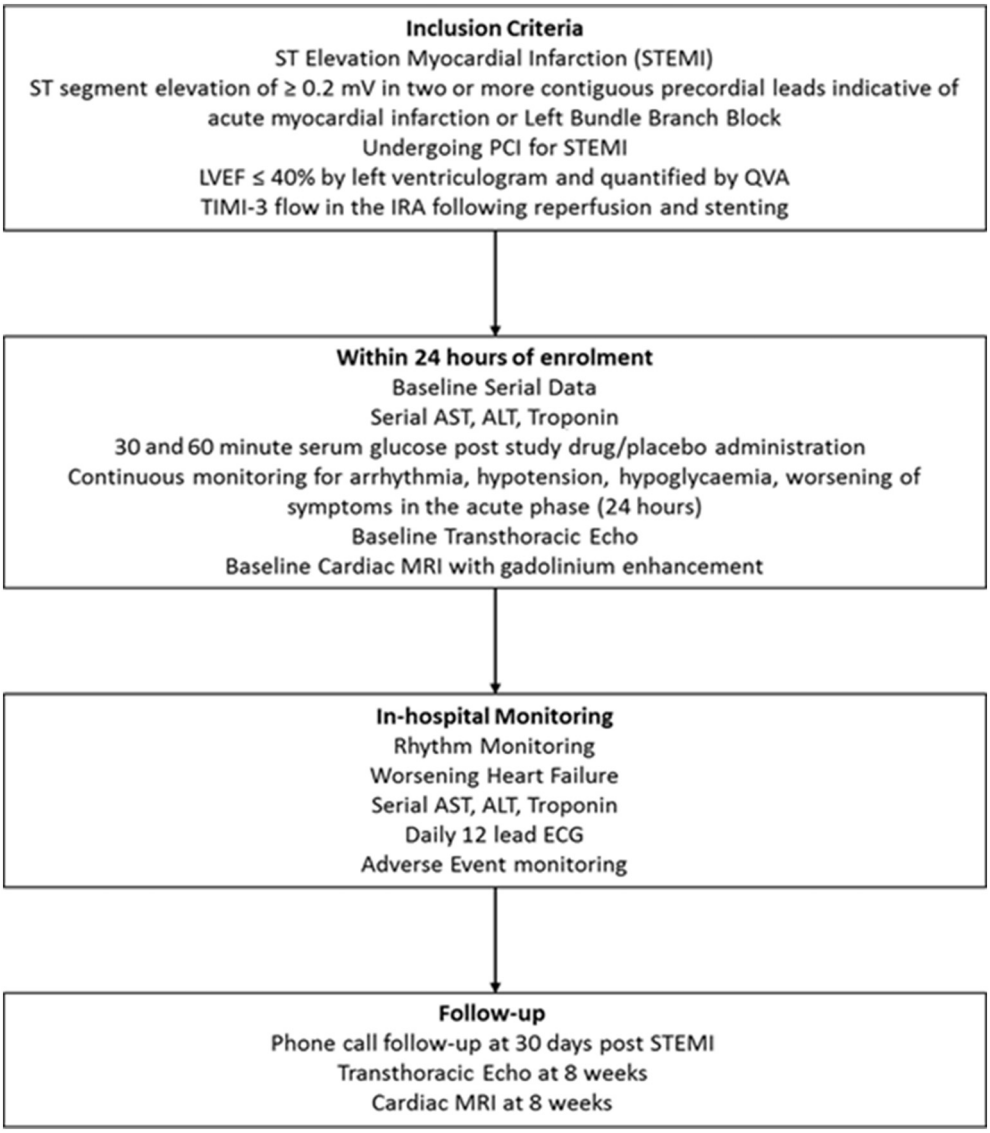

Figure 1. Study design.

to both treatment arms combined (15:30). Regarding adverse events, a sample size of 15 in a given arm would give a 95% CI of 0% to 22% for any nonobserved events.

Categorical data were described as counts and percentages, and continuous variables were described by their medians and interquartile ranges. For estimates of adverse event rates, binomial 95% CIs were calculated using the Pearson-Klopper method. Mean outcome differences between each treatment arm and placebo were estimated with analysis of covariance (ANCOVA) adjusted for baseline outcome and diabetes status at recruitment. We reported estimates, 95% CI, and the corresponding *P* values from the 2-sided test of the null hypothesis of no difference. Models were estimated using complete case samples, thus assuming that missing data were missing completely at random. Analyses were done on an intention-to-treat basis or on a modified intention-to-treat basis in the presence of missing data (and for no other reason). All analyses were conducted using the R Project for Statistical Computing version 3.2.[17]

Results

From 473 patients screened for eligibility, 47 patients agreed to participate and were randomized. The enrollment pathway and trial profile are shown in Figure 2. Most of the 426 patients excluded had systolic function that was greater than the threshold for study inclusion (LVEF <40%). Forty-six patients completed the 8-week follow-up. Baseline clinical characteristics did not statistically differ among treatment groups (Table I). Median time from symptom onset to PCI was 4 hours and from initiation of PCI to drug administration was approximately 70 minutes and did not vary among groups. The overall mean time from final balloon inflation to drug administration was 23.8 minutes. The per-arm means were as follows: placebo, 19.6 minutes; 1.5 ng IGF1, 25.9 minutes; 15 ng IGF1, 25.6 minutes. Although the mean times in the 2 active treatment arms were about 6 minutes greater than placebo, the data were consistent with the null hypothesis in that there was no statistically significant difference between the groups (ANOVA $P = .52$). Use of thrombolysis was variable between treatment groups, but TIMI flow prior to PCI was not significantly different statistically among groups, and all patients enrolled had TIMI 3 flow after PCI (Table I).

LV dysfunction (mean LVEF) on LV angiogram prior to drug administration was similar in all groups (Table I). During hospital stay or at discharge, there was also no significant difference in medications between groups, and all patients adhered to their discharge medical regimen as determined at 30-day phone follow-up (Table I).

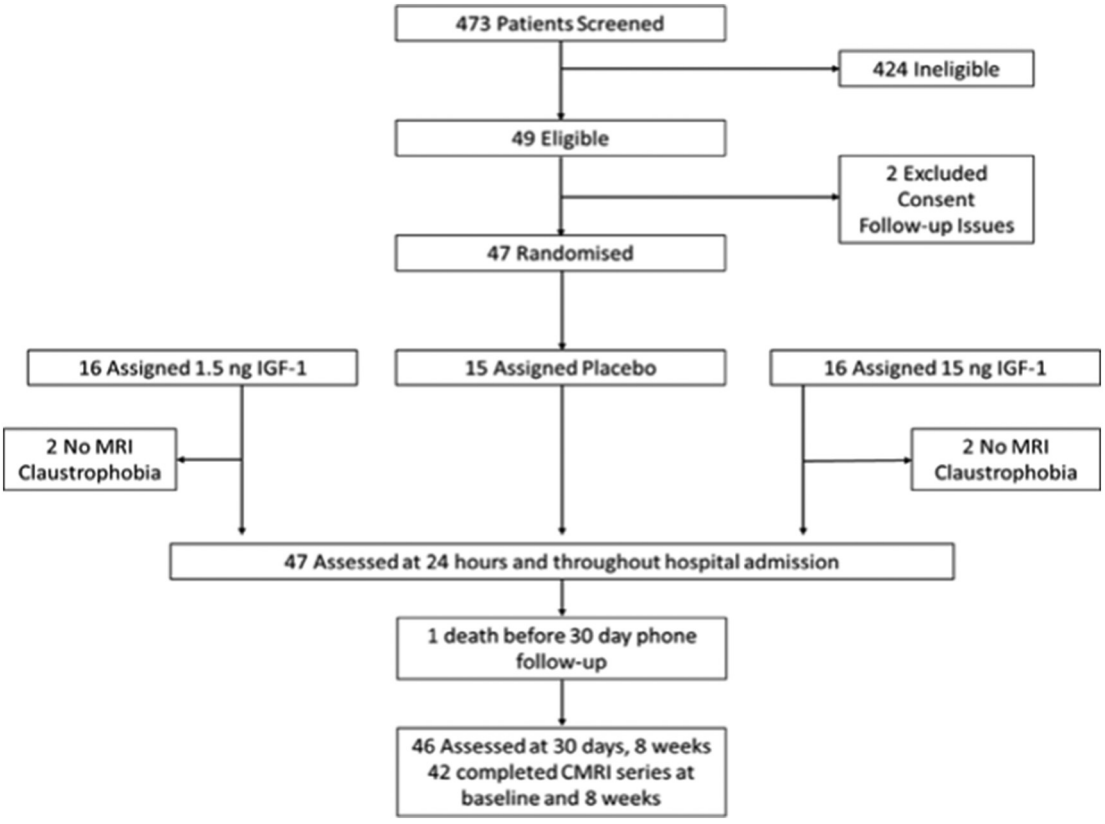

Figure 2. Trial profile.

None of the prespecified safety end points (hypoglycemia, significant hypotension, or tachyarrhythmia) occurred in the first 1 hour after study drug administration (Table II). With respect to adverse effects previously reported for human growth hormone, no patient (0/47) in the study reported jaw discomfort, arthralgia, or persistent headache out to 30 days post drug administration. With respect to prespecified clinical events in hospital, there was no significant difference between groups (Table II). Moreover, there was no significant difference in ischemic outcomes between groups out to 30-day follow-up (Table II).

There were 14 patients who experienced an arrhythmia (29% of 47 patients, 95% CI 17%-45%), with 4 in the placebo arm, 5 in the 1.5-ng IGF1 arm, and 5 in the 15-ng IGF1 arm. Eight arrhythmias occurred on the day of the procedure: 3 at +1 day, 2 at +2 days, and 1 at +3 days. There were also 1 recurrent MI (+284 days) in the 15-ng IGF1 arm, 1 recurrent severe ischemia (+93 days) in the 1.5-ng IGF1 arm, and 1 death (+14 days) in the 15-ng IGF1 arm (total sample 95% CIs for these singular events are 0%-11%). There was no target vessel revascularization (total sample 95% CIs for nonobserved events are 0%-7.5%), and there were no significant differences in the event rate across study arms out to 30 days (χ^2 test P value = .77). The 1 patient death occurred at day 10 post-MI, and the patient died while sleeping at home 3 days after hospital discharge. The death was presumed to be due to ventricular arrhythmia, and no autopsy was performed.

Forty-two patients had cardiac MRI performed at baseline and 8 weeks, with 5 patients having no MRI data due to claustrophobia (4 patients) and 1 death (Figure 2). One additional patient had an MRI of insufficient quality due to incomplete breath-hold because of pulmonary congestion during the baseline scan. Baseline and 8-week MRI data are presented for placebo, 1.5-ng IGF1, and 15-ng IGF1 patients on Figure 3 and Table III. Forty-one patients had complete MRI data suitable for GLVEF, LV volumes, mass, and stroke volume analysis both at baseline and at 8 weeks. Eleven patients had scans that were not suitable for late gadolinium enhancement analysis all due to inadequate prolonged breath-hold at the end of the scan at baseline (8 patients) and at 8 weeks (3 patients). Thirty-one patients had gadolinium enhancement suitable for infarct size analysis both at baseline and at 8 weeks.

There was no apparent impact of treatment on the primary efficacy end point. Mean GLVEF at 24 hours posttreatment was 39.4% (7.5 SD) in the placebo arm and 41.2% (9.5) and 44.9% (8.0) in IGF1 1.5-ng and 15-ng arms, respectively. This increased after 2 months in all 3 arms to 45.9% (5.8), 48.5% (13.5), and 50.2% (9.6), respectively (Figure 3). The difference in adjusted mean GLVEF compared to placebo was 1.76% (95% CI −3.35 to 6.87; $P = .51$) for 1.5 ng IGF1 and −0.90% (95% CI −6.09 to 4.29; $P = .74$) for 15 ng IGF1. With reference to the assumptions underpinning the sample size calculation, GLVEF was more variable than expected, and there was a larger than anticipated improvement in GLVEF in the placebo arm.

With regard to secondary efficacy end points compared with placebo, the 15-ng IGF1 treatment was associated with a significant reduction in LV end-diastolic volume index (−16.38 mL/m^2, 95% CI −29.30 to −3.46; $P = .018$), LV mass index (−15.48 g/m^2, 95% CI −23.97 to −7.00; $P = .001$), and stroke volume (−16.02 mL, 95% CI −28.49 to −3.56; $P = .016$). There were no apparent differences in any of these end points between the placebo and the IGF1 1.5-ng arms (Table III).

There was a nonsignificant reduction in late contrast enhancement (LateCE) in the higher-dose 15-ng IGF1 patients compared to the other 2 groups (95% CI −22.3 to 1.4, $P = .095$) (Table III). Using the Benjamini-Hochberg procedure to adjust for multiple comparisons, by controlling the false discovery rate at 5%, all 3 secondary effects above remained significant for the higher-dose IGF1 group when adjusted based on the ANCOVA P values.

Discussion

This randomized, double-blind, placebo-controlled clinical trial is the first to evaluate the safety and cardioprotective effects of low-dose IGF1 in STEMI patients. Although there were no safety concerns, the

Table I
Baseline characteristics

Variable	Total (n = 47)	Placebo (n = 15)	IGF1 1.5ng (n = 16)	IGF1 15ng (n = 16)	Test *P* value
Age (y)	59 (50-66)	55 (51.5-66)	57.5 (45.8-65.5)	61.5 (52.2-65.2)	.78
Sex					.57
Male	37 (78.7%)	11 (73.3%)	12 (75%)	14 (87.5%)	
Female	10 (21.3%)	4 (26.7%)	4 (25%)	2 (12.5%)	
Smoking					.88
0	11 (23.4%)	3 (20%)	3 (18.8%)	5 (31.2%)	
1	10 (21.3%)	4 (26.7%)	3 (18.8%)	3 (18.8%)	
2	26 (55.3%)	8 (53.3%)	10 (62.5%)	8 (50%)	
Hypertension					.97
No	27 (57.4%)	9 (60%)	9 (56.2%)	9 (56.2%)	
Yes	20 (42.6%)	6 (40%)	7 (43.8%)	7 (43.8%)	
Dyslipidemia					.11
No	37 (78.7%)	14 (93.3%)	10 (62.5%)	13 (81.2%)	
Yes	10 (21.3%)	1 (6.7%)	6 (37.5%)	3 (18.8%)	
Diabetes					.32
No	44 (93.6%)	13 (86.7%)	16 (100%)	15 (93.8%)	
Yes	3 (6.4%)	2 (13.3%)	0 (0%)	1 (6.2%)	
Family history of cardiac disease					.05
No	30 (68.2%)	12 (80%)	6 (42.9%)	12 (80%)	
Yes	14 (31.8%)	3 (20%)	8 (57.1%)	3 (20%)	
SBP (mm Hg)	118 (106-126.5)	128 (108.5-142.5)	118 (103.8-124.2)	113.5 (104.5-119.2)	.17
DBP (mm Hg)	75 (67-84.5)	76 (70.5-86.5)	73.5 (70-84.5)	72.5 (60-81.5)	.51
Heart rate (beat/min)	84 (72.5-94.5)	85 (76.5-97)	82 (70.8-91.8)	83.5 (74.5-90)	.46
Height (cm)	172.7 (167-179)	170.2 (168.5-180.5)	170 (163-174.8)	174.9 (172-178.5)	.18
Weight (kg)	76.2 (69.9-90)	71.1 (62.5-92.7)	75.5 (66.5-82.1)	81.2 (75.2-90)	.25
BMI (kg/m^2)	25.4 (22.8-28.5)	23 (21.3-28.5)	24.7 (23.1-28.4)	26 (25.3-28.9)	.4
TIMI flow prior to PCI					.11
0	23 (50%)	10 (66.7%)	9 (60%)	4 (25%)	
1	4 (8.7%)	2 (13.3%)	0 (0%)	2 (12.5%)	
2	6 (13%)	2 (13.3%)	1 (6.7%)	3 (18.8%)	
3	13 (28.3%)	1 (6.7%)	5 (33.3%)	7 (43.8%)	
Infarct-related artery					.34
LAD	46 (97.9%)	14 (93.3%)	16 (100%)	16 (100%)	
LCx	1 (2.1%)	1 (6.7%)	0 (0%)	0 (0%)	
Thrombolysis prior to PCI					.23
No	42 (89.4%)	15 (100%)	13 (81.2%)	14 (87.5%)	
Yes	5 (10.6%)	0 (0%)	3 (18.8%)	2 (12.5%)	
Post-PCI LVEF	37.1 (33.3-38.9)	36.9 (34.5-38.5)	35 (27.8-38.4)	37.8 (35.3-38.8)	.39
Stent type					.83
DES	33 (70.2%)	12 (80%)	10 (62.5%)	11 (68.8%)	
BMS	4 (8.5%)	1 (6.7%)	2 (12.5%)	1 (6.2%)	
Bioabsorbable DES	10 (21.3%)	2 (13.3%)	4 (25%)	4 (25%)	
Baseline Killip					.21
1	40 (87%)	13 (92.9%)	15 (93.8%)	12 (75%)	
2	6 (13%)	1 (7.1%)	1 (6.2%)	4 (25%)	
Peak troponin T (HS ng/L) post-PCI	5790 (3109-8577)	6183 (4174-8940)	5900 (3884-9212)	5389 (1876-7993)	.87
Ischemia to PCI (min)	255 (200-399)	240 (209-323)	254 (222-414)	279 (181-451)	.83
Time from start of PCI to drug administration (min)	71 (57-86)	62 (57.5-79)	76.5 (57.5-93.5)	79 (55-87.2)	.7
Medications					
Antiplatelet					
ASA	47 (100%)	15 (100%)	16 (100%)	16 (100%)	-
Clopidogrel	18 (38.3%)	9 (60%)	3 (18.8%)	6 (37.5%)	.06
Prasugrel	16 (34%)	3 (20%)	8 (50%)	5 (31.2%)	.2
Ticagrelor	13 (29.8%)	3 (20%)	5 (31.2%)	5(31.2%)	.72
GPIIb/IIIa antagonist	26 (56.5%)	8 (53.3%)	8 (53.3%)	10 (62.5%)	.84
2° Prevention					
β-Blocker	47 (100%)	15 (100%)	16 (100%)	16 (100%)	-
Statin	47 (100%)	15 (100%)	16 (100%)	16 (100%)	-
Heart failure					
ACEI	42 (89.4%)	14 (93.3%)	13 (81.2%)	15 (93.8%)	.43
Aldosterone antagonist	17 (36.2%)	5 (33.3%)	5 (31.2%)	7 (43.8%)	.73
NYHA at discharge					.94
1	28 (59.6%)	9 (60%)	10 (62.5%)	9 (56.2%)	
2	19 (40.4%)	6 (40%)	6 (37.5%)	7 (43.8%)	

SBP, systolic blood pressure; *DBP*, diastolic blood pressure; *BMI*, body mass index; *LAD*, left anterior descending; *LCx*, left circumflex; *DES*, drug-eluting stent; *BMS*, bare metal stent; *ASA*, acetylsalicylic acid; *ACEI*, angiotensin-converting enzyme inhibitor.

primary efficacy end point of greater enhancement in global LV systolic function was not met for either dose of IGF1 compared to placebo. In control and IGF1-treated subjects, LVEF increased over the 2-month follow-up consistent with prior revascularization trials using thombolytics or PCI.[18-20] With regard to secondary outcomes, 15 ng IGF1 significantly reduced LV volume (LVEDVI) in addition to attenuation of LV mass and stroke volume increases compared to 1.5 ng IGF1 and placebo.

The safety of both low doses of IGF1 in this trial is not surprising given that the concentrations of drug used were 100,000-fold less

Table II
Safety end points

	Placebo	IGF1 1.5 ng	IGF1 15 ng
	n = 15	n = 16	n = 16
Hemodynamic and blood glucose parameters			
Hypotension	0	0	0
Tachycardia	0	0	0
Hypoglycemia	0	0	0
Arrhythmias in the first 24 h			
Supraventricular tachycardia	0	0	0
Atrial fibrillation	2	1	2
Atrial flutter	0	0	0
Ventricular tachycardia	0	0	0
Nonsustained ventricular tachycardia	1	2	1
Ventricular fibrillation	0	0	0
Arrhythmias during rest of hospital admission			
Supraventricular tachycardia	0	0	0
Atrial fibrillation	2	0	2
Atrial flutter	0	0	0
Ventricular tachycardia	1	0	0
Nonsustained ventricular tachycardia	0	0	0
Ventricular fibrillation	0	0	0
Subacute ischemic outcomes to 30 d			
Death	0	0	1
Recurrent MI	0	0	0
Repeat revascularization IRA	0	0	0
Heart failure	0	0	0
Stroke	0	0	0

There were no significant differences in the prespecified safety event rates across study arms out to 30 days (χ^2 test P value = .77).

than doses previously proven safe to administer to normal human volunteer subjects (personal communication; Increlex manufacturer's brochure). We were concerned specifically about acute (within the first hour of IC administration) glycemic, hypotensive, and tachycardia adverse effects, none of which occurred in the 32 subjects who received IGF1. As IGF1 has a half-life of 14 minutes in the circulation, we anticipated that adverse effects would most likely manifest early postinjection. Moreover, there was no increase in later arrhythmias or any other major adverse cardiac events in the IGF1-treated subjects compared to placebo-treated controls. We paid particular attention to hGH (which mediates effects through IGF1)-like adverse effects such as myalgia, arthralgia, headache, and jaw pain, all of which were not detected in any of the groups studied. There was 1 death in the higher-IGF1–treated group (15 ng), but this patient died at day 10 post-STEMI presumably of ventricular arrhythmia, and it was felt that this did not relate to IGF1 treatment given the time of death and the known risk of ventricular arrhythmia in patients with LVEF <40% post-STEMI. Thus, this pilot study suggests that IGF1 at the doses administered in this trial is safe in the setting of acute STEMI.

The rationale for evaluating the efficacy of intracoronary IGF1 in improving cardiac remodeling in patients undergoing myocardial infarction was based on experimental evidence supporting a key role of low-dose IGF1 in initiating cardiomyocyte cytoprotection in the presence of reperfusion injury.[5,9,10,14] Briefly, in a porcine model of 90-minute LAD occlusion and 2 hours into reperfusion, IGF 1 at the lower dose range (1.5 ng) used in this study improved cardiomyocyte survival and 2-month remodeling of LV compared to placebo post experimental infarction.[5] Parallel signaling studies performed at 30 minutes post IGF1 injection indicated specific phosphorylation of cognate IGF1 receptor in cardiomyocytes in the infarct/border zone. Apoptotic assays at 24 hours indicated that cell death was effectively inhibited in the infarct border zone which abrogated later inflammatory and fibrotic changes in the infarcted heart.[5]

Moreover, previous preclinical porcine work had shown that IGF1 in conditioned media at concentrations similar to the lower dose used in this trial was in part responsible for the cardioprotective effect of paracrine factors secreted from endothelial progenitor cells.[21,22] The timing of IGF1 injection in patients was also based on this preclinical experience where early injection of conditioned media in the reperfusion phase post infarct injury successfully attenuated acute cardiomyocyte death, early inflammation, and later scar formation and adverse LV dilatation post-MI.[22] The reason why these promising preclinical data[5,22] were not predictive in the current human trial may relate to the complexity and heterogeneity of the human disease as well as reduced intersubject variability in the porcine model used.

Given the short half-life of IGF1,[23] it is possible that some secondary efficacy effects seen in this trial may have been initiated early after injection. Experimental models have previously indicated that exogenous IGF1 delivered via the infarct-related artery enters at-risk myocardium within minutes, most likely through permeable microvasculature in the infarct and border zones.[5] This event initiates a signaling cascade in cardiomyocytes presenting IGF1 receptor, which includes Akt/PI3 kinase and GSK3β prosurvival pathways,[5] the latter being implicated in regulation of crucial mitrochondrial permeability-transition pore function.[5] In this way, early cytoprotection especially in the infarct border zone may act as a bulwark against further infarct expansion and

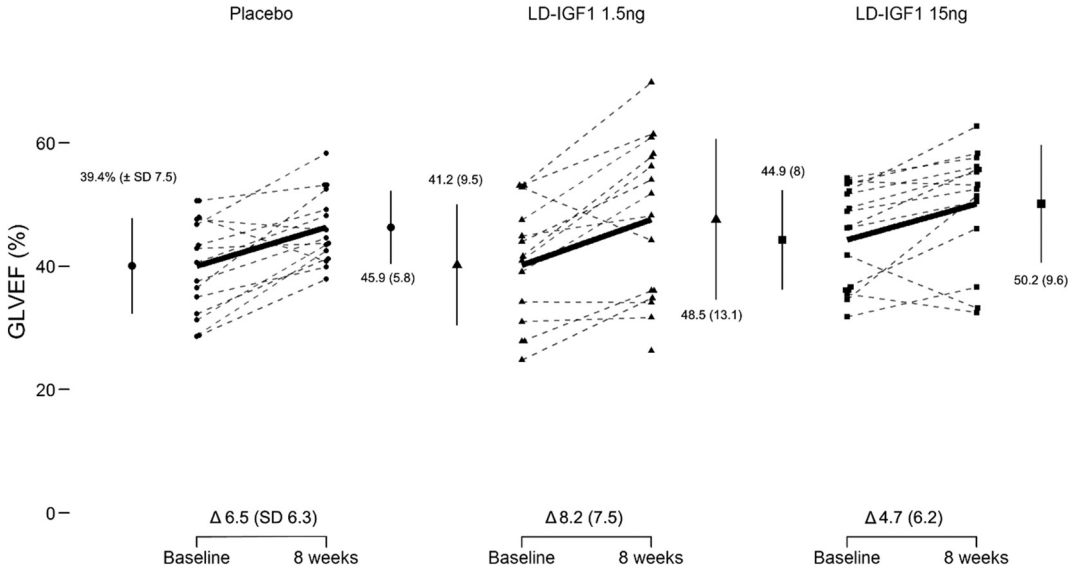

Figure 3. Treatment effect of IGF1 and placebo on GLVEF.

Table III
Secondary efficacy end points

	Baseline		8 wk		Change		ANCOVA		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Estimate*	95%CI	*P*
LVEDV index (mL/m^2)									
Placebo	14	96 (16.2)	14	114.5 (20.6)	14	18.5 (14.2)		Ref	
IGF1 1.5 ng	13	98.6 (17.3)	15	105.1 (22.4)	13	9.1 (18)	−10.251	(−23.495 to 2.992)	.138
IGF1 15 ng	15	93.6 (9.7)	14	95 (24)	14	2.3 (18.9)	−16.383	(−29.304 to −3.462)	.018
LVESV index (ml/m^2)									
Placebo	14	58.7 (15)	14	62.2 (14.6)	14	3.6 (10.3)		Ref	
IGF1 1.5 ng	13	58.8 (17.3)	15	55.4 (21.5)	13	−2.6 (15.5)	−6.594	(−16.85 to 3.663)	.216
IGF1 15 ng	15	51.8 (10.4)	14	49.5 (19.2)	14	−1.2 (13.4)	−5.351	(−15.611 to 4.908)	.313
LV mass index (g/m^2)									
Placebo	10	85.8 (17)	12	85 (14.8)	9	0.5 (8.6)		Ref	
IGF1 1.5 ng	9	93 (17.1)	12	90.8 (7.2)	8	−2 (13.4)	−1.083	(−10.663 to 8.498)	.827
IGF1 15 ng	15	92.5 (19.9)	13	75.9 (18.4)	13	−17 (13.4)	−15.484	(−23.969 to −6.998)	.001
Stroke volume (mL)									
Placebo	14	71.4 (20.3)	14	99.9 (26.1)	14	28.4 (17.8)		Ref	
IGF1 1.5 ng	13	74.2 (17.4)	15	92 (27)	13	21.6 (17.2)	−7.801	(−20.123 to 4.521)	.223
IGF1 15 ng	15	83.6 (15.7)	14	94.8 (14.9)	14	10.9 (14.1)	−16.024	(−28.487 to −3.56)	.016
Late CE									
Placebo	10	56.2 (29)	12	49.1 (19.3)	9	−12.5 (20.4)		Ref	
IGF1 1.5 ng	10	59.2 (34.3)	12	47.4 (22.4)	9	−12.4 (21.2)	−1.089	(−14.022 to 11.845)	.87
IGF1 15 ng	15	56.8 (48.7)	13	34.5 (29.6)	13	−18.2 (26.2)	−10.448	(−22.254 to 1.359)	.095

* Expressed as differences (vs placebo) in adjusted means (ANCOVA, adjusted for baseline outcome and diabetes status) with corresponding 95% CIs and *P* value from the 2-sided test of no difference.

maladaptive LV remodeling in the months postinfarction. For instance, later cavity expansion is associated with compensatory hypertrophy increasing LV mass with attendant increases in stroke volume, both of which are potentially indicators of maladaptive remodeling and may contribute to long-term heart failure.[24,25] The strong trend to reduced infarct size in the 15-ng IGF1 group would support an early cytoprotective effect of IGF1 and is consistent with previous preclinical observations in multiple experimental models.[5,9,10,14,21,22]

The major limitations of this pilot study include small sample size, variability in LVEF and other baseline characteristics especially pre-PCI thrombolysis TIMI 3 flow rate, and the significant dropout rate of late gadolinium enhancement determination in 11 patients. Together, these limitations give insufficient power to determine the full clinical efficacy of intracoronary IGF1. The attained versus expected % change in LVEF from baseline to 8 weeks was 8 (±5) versus 8.2 (±7.5) for 15-ng IGF1 dose and 2.2 (±5) versus 6.5 (±6.3) for placebo, so LVEF as a parameter was more variable than expected, and the change in placebo was larger than expected. Thus, future studies to test 15 ng IGF1 versus placebo, based on the effect size and variance seen in the current trial, would require 200 subjects in each arm with power = 0.8 and α = .05 based on *t* test with common variance. There was variability in the DES stents used, and acute pharmacotherapy including thrombolytics, IIb/IIIa antagonists used, although none of these parameters reached statistical significance in terms of group differences (Table I). Despite this, it is likely that any future studies evaluating IGF1 should restrict patients to those with TIMI 0/1 flow on presentation, and guidance on pharmacotherapy and stent treatment should aim to reduce intersubject variability to a minimum. This current study reflected real-world practice and left PPCI management of patients in catheterization laboratory to the discretion of the interventional cardiologist.

Approximately 25% (11/42) of patients had gadolinium enhancement images unsuitable for analysis primarily due to difficulties in sustaining adequate breath-holding especially at the 24-hour baseline scan (8/11). In future studies, it may therefore be beneficial to perform baseline scanning at 3 days rather than 24 hours post-MI. Eight weeks was used as the follow-up interval for repeat MRI based on previous large-animal data. It may have been useful to look at a later time point of 4 months where noninfarct remodeling becomes more evident in terms of EDV and LV mass. We hope to capture some of these data in future analysis of 6-month echocardiography follow-up (not included here). Among patients missing any outcome data, there were no apparent differences from those with no missing data with respect to the patient characteristics reported in Table I. Moreover, there were no appreciable differences when comparing patients who were missing any late CE data at baseline or 8 weeks (Supplementary Table 1). We cannot exclude the possibility of differences in unmeasured variables such as complexity of coronary artery disease or clinical risk scores. There was no statistically significant difference in peak troponins between treatment groups, but temporal tracking of acute cardiomyocyte death (troponin release profile) was not specified as an efficacy end point, and thus, it is not clear whether IGF1 had any acute prosurvival effect. Given the previous safety profile of many log-fold higher doses of IGF1 in normal and IGF1-deficient human subjects (personal communication; Increlex manufacturers brochure), it is conceivable that higher doses of IGF1 than used in this study would be safe and may have additional therapeutic potential. Moreover, slow-release IGF1 preparations or sequential dosing over time may extend the temporal window for therapeutic efficacy of this cytoprotective approach especially given that cardiomyocyte death is an ongoing process in the 24-72 hours postinfarction.[26] Finally, it is likely that increasing LVEF entry threshold to <45% may have enhanced enrolment and reduced the large number of screening failures in this trial.

In conclusion, this study suggests that low-dose IGF1 is safe when administered via the intracoronary route in the setting of STEMI undergoing PPCI. The failure to achieve a positive primary outcome added to several study limitations indicates that our secondary outcome data results can only be viewed as exploratory. Acknowledging design limitations in the current study, any future trial involving a larger number of patients should aim to reduce the variability in clinical presentation (TIMI flow, ischemic time) and MRI (LVEF, gadolinium dropout) parameters observed in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.03.018.

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