# Statistical methods

The sample size of 15 patients in each arm was based on an expected improvement in GLVEF of 8 percentage points in the patients treated with 1.5ng LD-IGF-1 vs. a 2.2 percentage point increase in the placebo arm, with a shared SD of 5 percentage points. Under these assumptions and alpha of 0.05, we would detect the anticipated difference between the placebo and 1.5ng LD-IGF-1 arms (15:15) with a power of 0.84; while the power would be 0.94 if comparing placebo to both treatment arms combined (15:30).

Categorical data were described as counts and percentages, and continuous variables were described by their medians and IQRs.

Mean outcome differences between each treatment arm and placebo were estimated with ANCOVA, adjusted for baseline outcome and diabetes status at recruitment. We reported estimates, 95% confidence intervals (CI), and the corresponding p-values from the two-sided test of the null hypothesis of no difference.  Models were estimated using complete case samples, thus assuming missing data were missing completely at random. Analyses were done on an intention-to-treat basis. All analyses were conducted using the R Project for Statistical Computing (version 3.2.2).

# Results

DESCRIBE RECRUITMENT/RANDOMIZATION (Figure 1). Baseline characteristics were similar across study arms (Table 1).

NEEDS EXPLANTION OF MISSING VALUES, PARTICULARLY FOR LVMASS INDEX AND LATE CE.

There were 14 arrhythmias (4 placebo, 5 low-dose, 5 high-dose), one recurrent MI (high-dose), one recurrent severe ischemia (low-dose), and one death (high-dose). There were no appreciable differences in the event rate across study arms (chi squared test p-value = 0.77).

There was no apparent impact of treatment on the primary outcome. Mean GLVEF at 24 hrs post-treatment was 39.4% (7.5 SD) in the placebo arm, and 41.2% (9.5) and 44.9% (8.0) in LD-IGF1 1.5ng and 15ng arms respectively. This increased after 2 months in all three arms to 45.9% (5.8), 48.5% (13.5), and 50.2% (9.6) respectively (Figure 2). The difference in adjusted mean GLVEF compared to placebo was 1.76% (95% CI -3.35 to 6.87; p = 0.51) for LD-IGF1 1.5ng, and -0.90% (95% CI -6.09 to 4.29; p = 0.74) for LD-IGF1 15ng (Table 2). 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.

Compared with placebo, the LD-IGF1 15ng treatment was associated with a significant improvement in LV end-diastolic volume index (-16.38 ml/m2, 95% CI -29.30 to -3.46; p = 0.018), LV mass index (-15.48 g/m2, 95% CI -23.97 to -7.00; p = 0.001) and stroke volume (-16.02 ml, 95% CI -28.49 to -3.56; p = 0.016). There were no apparent differences in any outcomes between the placebo and the LD-IGF1 1.5ng arms (Table 2).

**Discussion**

The study was not well powered to detect changes in the primary outcome, as the improvement in GLVEF seen in the placebo arm, as well as the variability of GLVEF, were higher than expected. To detect the difference in GLVEF improvement we expected in the treatment arms, given the change in the placebo arm and variability we actually observed, a subsequent study would likely need 200 patients in each arm to achieve a power of 0.8 with alpha = 0.05.

Figure 2. Changes in GLVEF (%) from baseline to 8 weeks in the three study arms.



TABLE 1. Baseline Characteristics

| **Variable** | **Total**  **(n = 47)** | **Placebo**  **(n = 15)** | **Low dose**  **(n = 16)** | **High dose**  **(n = 16)** |
| --- | --- | --- | --- | --- |
| Age (years) | 59 [50, 66] | 55 [51.5, 66] | 57.5 [45.8, 65.5] | 61.5 [52.2, 65.2] |
| Sex |  |  |  |  |
| 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 |  |  |  |  |
| 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%) |
| Hyptertension | 20 (42.6%) | 6 (40%) | 7 (43.8%) | 7 (43.8%) |
| Dyslipidemia | 10 (21.3%) | 1 (6.7%) | 6 (37.5%) | 3 (18.8%) |
| Diabetes | 3 (6.4%) | 2 (13.3%) | 0 (0%) | 1 (6.2%) |
| Family history of  cardiac disease | 14 (31.8%) | 3 (20%) | 8 (57.1%) | 3 (20%) |
| SBP (mmHg) | 118 [106, 126.5] | 128 [108.5, 142.5] | 118 [103.8, 124.2] | 113.5 [104.5, 119.2] |
| DBP (mmHg) | 75 [67, 84.5] | 76 [70.5, 86.5] | 73.5 [70, 84.5] | 72.5 [60, 81.5] |
| Heart rate (bpm) | 84 [72.5, 94.5] | 85 [76.5, 97] | 82 [70.8, 91.8] | 83.5 [74.5, 90] |
| Height (cm) | 172.7 [167, 179] | 170.2 [168.5, 180.5] | 170 [163, 174.8] | 174.9 [172, 178.5] |
| Weight (kg) | 76.2 [69.9, 90] | 71.1 [62.5, 92.7] | 75.5 [66.5, 82.1] | 81.2 [75.2, 90] |
| BMI (kg/m2) | 25.4 [22.8, 28.5] | 23 [21.3, 28.5] | 24.7 [23.1, 28.4] | 26 [25.3, 28.9] |
| TIMI flow prior to PCI |  |  |  |  |
| 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 |  |  |  |  |
| 1 | 46 (97.9%) | 14 (93.3%) | 16 (100%) | 16 (100%) |
| 2 | 1 (2.1%) | 1 (6.7%) | 0 (0%) | 0 (0%) |
| Thrombolysis prior to PCI | 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] |
| Stent Type |  |  |  |  |
| 1 | 33 (70.2%) | 12 (80%) | 10 (62.5%) | 11 (68.8%) |
| 2 | 4 (8.5%) | 1 (6.7%) | 2 (12.5%) | 1 (6.2%) |
| 3 | 10 (21.3%) | 2 (13.3%) | 4 (25%) | 4 (25%) |
| Baseline KILIP |  |  |  |  |
| 1 | 40 (87%) | 13 (92.9%) | 15 (93.8%) | 12 (75%) |
| 2 | 6 (13%) | 1 (7.1%) | 1 (6.2%) | 4 (25%) |
| Ischemia to PCI (hr) | 4[3, 7] | 4 [3, 5] | 4 [4, 7] | 5 [3, 8] |
| Time from PCI to drug  administration (min) | 71 [57, 86] | 62 [57.5, 79] | 76.5 [57.5, 93.5] | 79 [55, 87.2] |
| NYHA at discharge |  |  |  |  |
| 1 | 28 (59.6%) | 9 (60%) | 10 (62.5%) | 9 (56.2%) |
| 2 | 19 (40.4%) | 6 (40%) | 6 (37.5%) | 7 (43.8%) |

TABLE 2.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | | | | |
|  | **Baseline** | | **8 Weeks** | | **Change** | | **ANCOVA** | | |
|  | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **Est\*** | **95%CI** | **p** |
| **LVEDV Index (ml/m2)** |  |  |  |  |  |  |  |  |  |
| Placebo | 14 | 96 (16.2) | 14 | 114.5 (20.6) | 14 | 18.5 (14.2) |  | ref |  |
| LD-IGF1 1.5 ng | 13 | 98.6 (17.3) | 15 | 105.1 (22.4) | 13 | 9.1 (18) | -10.25 | (-23.50 to 2.99) | 0.138 |
| LD-IGF1 15 ng | 15 | 93.6 (9.7) | 14 | 95 (24) | 14 | 2.3 (18.9) | -16.38 | (-29.30 to -3.46) | 0.018 |
| **LVESV Index (ml/m2)** |  |  |  |  |  |  |  |  |  |
| Placebo | 14 | 58.7 (15) | 14 | 62.2 (14.6) | 14 | 3.6 (10.3) |  | ref |  |
| LD-IGF1 1.5 ng | 13 | 58.8 (17.3) | 15 | 55.4 (21.5) | 13 | -2.6 (15.5) | -6.59 | (-16.85 to 3.66) | 0.216 |
| LD-IGF1 15 ng | 15 | 51.8 (10.4) | 14 | 49.5 (19.2) | 14 | -1.2 (13.4) | -5.35 | (-15.61 to 4.91) | 0.313 |
| **GLVEF (%)** |  |  |  |  |  |  |  |  |  |
| Placebo | 14 | 39.4 (7.5) | 14 | 45.9 (5.8) | 14 | 6.5 (6.3) |  | ref |  |
| LD-IGF1 1.5 ng | 13 | 41.2 (9.5) | 15 | 48.5 (13.1) | 13 | 8.2 (7.5) | 1.76 | (-3.36 to 6.87) | 0.505 |
| LD-IGF1 15 ng | 15 | 44.9 (8) | 14 | 50.2 (9.6) | 14 | 4.7 (6.2) | -0.90 | (-6.09 to 4.29) | 0.736 |
| **LV Mass Index (g/m2)** |  |  |  |  |  |  |  |  |  |
| Placebo | 10 | 85.8 (17) | 12 | 85 (14.8) | 9 | 0.5 (8.6) |  | ref |  |
| LD-IGF1 1.5 ng | 9 | 93 (17.1) | 12 | 90.8 (7.2) | 8 | -2 (13.4) | -1.08 | (-10.66 to 8.50) | 0.827 |
| LD-IGF1 15 ng | 15 | 92.5 (19.9) | 13 | 75.9 (18.4) | 13 | -17 (13.4) | -15.48 | (-23.97 to -6.99) | 0.001 |
| **Stroke Volume (ml)** |  |  |  |  |  |  |  |  |  |
| Placebo | 14 | 71.4 (20.3) | 14 | 99.9 (26.1) | 14 | 28.4 (17.8) |  | ref |  |
| LD-IGF1 1.5 ng | 13 | 74.2 (17.4) | 15 | 92 (27) | 13 | 21.6 (17.2) | -7.80 | (-20.12 to 4.52) | 0.223 |
| LD-IGF1 15 ng | 15 | 83.6 (15.7) | 14 | 94.8 (14.9) | 14 | 10.9 (14.1) | -16.02 | (-28.49 to -3.56) | 0.016 |
| **Late CE** |  |  |  |  |  |  |  |  |  |
| Placebo | 10 | 56.2 (29) | 12 | 49.1 (19.3) | 9 | -12.5 (20.4) |  | ref |  |
| LD-IGF1 1.5 ng | 10 | 59.2 (34.3) | 12 | 47.4 (22.4) | 9 | -12.4 (21.2) | -1.08 | (-14.02 to 11.86) | 0.87 |
| LD-IGF1 15 ng | 15 | 56.8 (48.7) | 13 | 34.5 (29.6) | 13 | -18.2 (26.2) | -10.45 | (-22.25 to 1.36) | 0.095 |
|  | | | | | | | | | |

\* 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 two sided test of no difference.

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