The role of Glucagon-Like Peptide 1 Loading on periprocedural myocardial infarction During elective PCI (GOLD-PCI study): A randomized, placebo-controlled trial

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Background The incretin hormone glucagon-like peptide 1 (GLP-1) has been shown to protect against lethal ischemia-reperfusion injury in animal models and against nonlethal ischemia reperfusion injury in humans. Furthermore, GLP-1 receptor agonists have been shown to reduce major adverse cardiovascular and cerebrovascular events (MACCE) in large-scale studies. We sought to investigate whether GLP-1 reduced percutaneous coronary intervention (PCI)–associated myocardial infarction (PMI) during elective PCI.

Methods The study was a randomized, double-blind controlled trial in which patients undergoing elective PCI received an intravenous infusion of either GLP-1 at 1.2 pmol/kg/min or matched 0.9% saline placebo before and during the procedure. Randomization was performed in 1:1 fashion, with stratification for diabetes mellitus. Six-hour cardiac troponin I (cTnI) was measured with a primary end point of PMI defined as rise ≫×5 upper limit of normal (280 ng/L). Secondary end points included cTnI rise and MACCE at 12 months.

Results A total of 192 patients were randomized with 152 (79%) male and a mean age of 68.1 ± 8.9 years. No significant differences in patient demographics were noted between the groups. There was no difference in the rate of PMI between GLP-1 and placebo (9 [9.8%] vs 8 [8.3%], $P = 1.0$) or in the secondary end points of difference in median cTnI between groups (9.5 [0-88.5] vs 20 [0-58.5] ng/L, $P = .25$) and MACCE at 12 months (7 [7.3%] vs 9 [9.4%], $P = .61$).

Conclusions In this randomized, placebo-controlled trial, GLP-1 did not reduce the low incidence of PMI or abrogate biomarker rise during elective PCI, nor did it influence the 12-month MACCE rate which also remained low.

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Elective percutaneous coronary intervention (PCI) has been associated with cardiac troponin release in between 25% and 50% of cases. Troponin release is a sensitive measure of cardiomyocyte damage resulting from ischemia-reperfusion (IR) injury and side-branch loss during PCI.[1] This troponin elevation may be associated with increased morbidity and mortality.[2,3] Elective PCI has been established as a useful model of IR injury.[4] Many different agents including remote ischemic preconditioning, cyclosporine A, and insulin infusions[5-7] have been used to target cardiac IR injury in both elective and emergency settings. However, despite numerous clinical

trials of varying success, no therapy has been adopted into routine clinical practice.[8,9]

Glucagon-like peptide-1 (7-36) amide (GLP-1) is an incretin hormone that has emerged as a potential cardioprotective agent.[10-12] GLP-1 receptor agonists such as exenatide and liraglutide, available as treatment options for type 2 diabetes mellitus, act principally by augmenting insulin release from pancreatic β cells. Other hypoglycemic actions include a reduction in glucagon and delayed gastric emptying.[13] Liraglutide reduced the risk of major adverse cardiovascular or cerebrovascular events (MACCE) when administered to a high-risk diabetic population.[14] Although much of this effect may reflect changes in atherosclerotic plaque composition and vulnerability, protection against myocardial ischemia may contribute to improved outcomes. Animal studies show that GLP-1 reduces myocardial infarct size in models of IR injury.[15-17] Exenatide improves myocardial salvage index after primary PCI for ST-elevation myocardial infarction,[18] whereas GLP-1 itself protects against myocardial stunning and cumulative ischemic dysfunction following nonlethal ischemia with both coronary balloon occlusion and dobutamine stress.[19-21]

The GOLD PCI trial was a single-center, randomized, double-blind, placebo-controlled trial to test the hypothesis that GLP-1 administered during elective PCI would reduce the incidence of lethal IR injury, measured by PCI-associated myocardial infarction (PMI) and cardiac troponin I (cTnI) rise.

Methods

Identification and recruitment of patients

Between March 2013 and March 2015, all patients undergoing elective PCI at a UK cardiothoracic center were screened for recruitment. Patients undergoing ad hoc PCI after diagnostic coronary angiography were not included. Patients aged ≫18 years attending for elective PCI, with capacity to give informed consent, were eligible to participate in the study. Exclusion criteria were recent myocardial infarction (≪6 weeks), creatinine ≫2.26 mg/dL, specified medication use (insulin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, GLP-1 receptor agonists, and nicorandil), women of childbearing age, and significant comorbidity (life expectancy ≪6 months). Eligible patients were given written information in advance of the procedure, providing written consent on the day of admission for PCI. Recruited patients were advised to avoid exercise that may precipitate angina for 24 hours prior to their procedure. Participants were randomized to receive either GLP-1 or matched placebo saline infusion.

Study infusions

GLP-1 (7-36) amide acetate (Bachem Distribution Services, Weil am Rhein, Germany) 100 μg, in lyophilized powder form, was dissolved into 50 mL 0.9% sodium chloride solution. This infusion or the placebo infusion (50 mL of 0.9% sodium chloride solution) was drawn up by 2 unblinded research nurses and passed to the blinded study investigators. The intravenous infusion was administered at a rate of 1.2 pmol/kg/min, beginning 30 minutes prior to the planned procedural start time and running until either the whole dose had been given, or up to a maximum infusion time of 6 hours. The maximum dose was therefore 100 μg. This dose was selected because it was effective in reducing myocardial stunning and cumulative ischemic dysfunction in the myocardium in a number of studies with few adverse effects.[19,21,22] Larger doses were associated with transient hypoglycemia and abdominal pain.[23]

Percutaneous coronary intervention

PCI was carried out using 5F-7F guide catheters, with radial access preferred. All patients received aspirin 300 mg. Patients who were not already taking dual antiplatelet therapy were administered clopidogrel 300 mg the evening prior to the procedure or clopidogrel 600 mg if given on the same day (at least 1 hour prior to the procedure). Patients who had previously undergone PCI for an acute coronary syndrome continued with ticagrelor or clopidogrel, with an additional bolus if judged necessary. Patients were anticoagulated with a heparin bolus after insertion of the arterial sheath (70-100 IU/kg), with later boluses titrated to maintain activated clotting time ≫250 seconds. Glycoprotein IIb/IIIa inhibitors were not used routinely but were available at operator discretion for bailout. No glycoprotein IIb/IIIa inhibitors were used in the study. All patients were treated with dual antiplatelet therapy for 12 months after drug-eluting stent implantation (or at least 4 weeks if a bare metal stent was used). Choice of interventional strategy was at the discretion of the treating interventional cardiologist. Procedural chest pain and ST-segment deviation ≫1 mm during coronary occlusion were recorded. Clinical follow-up of patients after their procedure was undertaken by the responsible interventional cardiologist.

Angiographic parameters

Coronary angiography and PCI were assessed using quantitative coronary angiography in 2 orthogonal planes. Lesions were reviewed by an interventional cardiologist blinded to treatment allocation using an offline CAAS workstation (Pie Medical Imaging, Maastricht, the Netherlands). Parameters measured included lesion length, reference vessel diameter, minimal luminal diameter, percentage stenosis (by area), and residual stenosis. Lesions were classified according to

American Heart Association/American College of Cardiology criteria.[24]

Myocardium at risk was assessed with reference to the target vessel using angiographic surrogates: a modified APPROACH score,[25] collateral vessel assessment (using the Rentrop score), and modified Jeopardy score.[26] Pre- and postprocedural assessments of epicardial flow (Thrombolysis in Myocardial Infarction [TIMI] coronary flow score) and microvascular integrity (TIMI myocardial blush grade) were also performed.[27]

Procedural information including fluoroscopic screening time, total procedure time, contrast dose, length and type of stent inserted, and duration and pressure of coronary balloon inflation were recorded, without prior knowledge of patient randomization.

Study biochemistry

Baseline blood samples for baseline cTnI, plasma glucose concentration, and creatine kinase–MB fraction (CKMB) were taken prior to administration of the study infusion; baseline complete blood count and biochemistry panel were also taken. Plasma glucose was measured again in all patients after insertion of the arterial sheath, and blood glucose measurements were repeated at least 2 hourly throughout the duration of the infusion as a safety measure. Postprocedural measurements of cTnI, CKMB, and serum creatinine were taken 6 hours after PCI was completed.

The first 20% (intended to be 80) of patients had samples taken for GLP-1, insulin, and free fatty acids (FFAs) (collectively known as the *metabolic bloods*) prior to GLP-1 infusion. Further metabolic bloods were taken immediately prior to the PCI procedure from the arterial sheath when GLP-1 had been administered for at least 30 minutes.

cTnI was measured using an automated chemiluminescent assay (Siemens LOCI Cardiac Troponin I assay, Germany). The analytical range of this assay is 17-40,000 ng/L, with the 99th percentile of a reference population (upper reference limit) at 56 ng/L.

Study end points

The primary end point of the trial was the incidence of PMI recorded at 6 hours postprocedure. The Third Universal Definition of Myocardial Infarction defines *PMI* as a rise in cTnI to 5× upper reference limit of a PCI procedure (280 ng/L) or a rise greater than 20%, should the baseline cTnI be elevated prior to the procedure.[28] Samples for cTnI were taken at baseline and 6 hours after the procedure. Secondary end points were rise in postprocedural cTnI, postprocedural CKMB, procedural chest pain score (measured on a visual analogue scale of 0 [no pain] to 10 [most severe discomfort ever experienced]), presence of ST-segment deviation $\gg$1 mm during coronary balloon occlusion, change in TIMI epicardial coronary flow score and TIMI myocardial blush grade, and rate of mortality and MACCE at 12-month follow-up. A subgroup of patients (intended to be the first 20%) underwent additional metabolic blood tests.

Major adverse cardiovascular and cerebrovascular events

The MACCE rate was a composite end point composed of all-cause death, nonfatal MI, stroke, hospitalization for unstable angina, or admission for heart failure. The end point was assessed by telephone calls at 6 and 12 months by an interviewer blinded to treatment allocation, confirmed from hospital and GP records, and by a committee blinded to treatment allocation, with an independent chairperson.

Statistical methods

Sample size

The sample size was determined for the primary end point: PMI rate at 6 hours post procedure. The CRISP stent trial, performed in the same institution, showed a PMI rate of approximately 50%.[4] This trial was performed with first-generation drug-eluting stents, which owing to larger strut size may have exacerbated the PMI rate. In addition, the criteria for PMI have become more stringent. Contemporary experience with second-generation drug-eluting stents suggested that the PMI rate was around 25%. To detect a 50% reduction in PMI rate from 25% to 12.5%, a power calculation indicated that 168 patients would be needed in each group (α = .05; β = 0.2); recruitment of 400 patients was planned to account for loss to follow-up and missing data.

Randomization

Patients were randomized using a computer-generated list provided by an independent statistician (Oxford University Consulting, UK). The protocol was a random permuted block randomization with varying block size of 4, 6, and 8 patients, stratified by the presence of diabetes mellitus. The randomization was performed and recorded by the pharmacist dispensing the GLP-1 or placebo.

Statistical methods

The trial adhered to Consolidated Standards of Reporting Trials (CONSORT) guidelines. All prespecified analyses were performed on an intention-to-treat basis. Statistical analysis was performed using R (version 3.4.1). Continuous data were subjected to assessment for normality; continuous non-normally distributed data were compared with the Wilcoxon rank-sum test and with Student *t* test for normally distributed data. The χ^2

was used for categorical variables, except when small counts meant that Fisher exact test was more appropriate.

The lead author had full access to and takes full responsibility for the integrity of the data. The trial database was locked prior to final analysis of the primary end point and all other secondary end points. Serious adverse events were reviewed by the trial's data monitoring committee. All authors have read and approved this manuscript. 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.

Data safety monitoring committee and trial oversight

The study was sponsored and monitored by the Royal Papworth Hospital NHS Foundation Trust. The trial was approved by the institutional board, the Cambridge Central Research Ethics Committee (REC No. 14/EE/0218), and the United Kingdom Medicine and Healthcare Regulatory Agency (EudraCT No. 2013-001967-22). The trial was registered with Clinicaltrials.gov (NCT02127996).

A nonblinded data safety monitoring committee was appointed to monitor study recruitment and trial safety. The committee conducted this analysis every 6 months as specified in the protocol. The committee was empowered to undertake interim analyses of data and make recommendations to a blinded trial steering committee regarding how the trial should proceed. The committee was independent of the investigators and included an independent statistician.

Funding

No extramural funding was used to support this work. Dr. Giblett's salary was provided using pump-priming funds at the Royal Papworth Hospital, and consumables were supported from the Cambridge BRC.

Results

Demographics, procedural, and metabolic data

Patient allocation in the study is detailed in a CONSORT diagram (Figure 1). Of 651 patients screened, 432 were eligible for recruitment to the study, from which 193 patients were randomized to receive either GLP-1 or placebo infusion. One patient was discovered to be ineligible after randomization and was excluded from the analysis. There was no crossover between the groups.

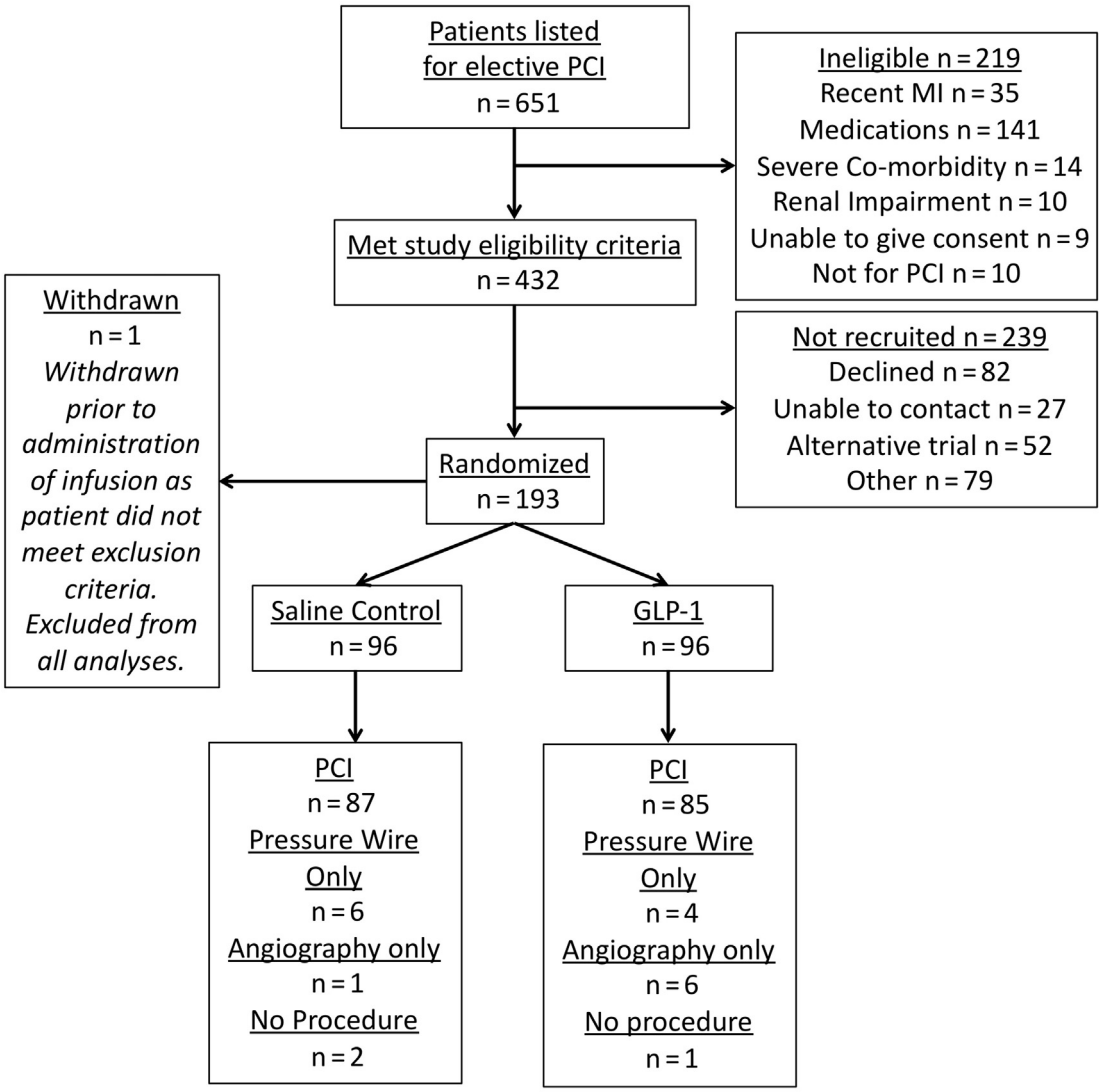
There were no statistically significant differences between the demographic characteristics of the groups (Table I). The proportion of patients with diabetes in the study was small (9.4%) but equal between groups as a result of the stratification. Procedural characteristics of patients in the study are also included in Table II; this shows that angiographic lesion complexity and lesion distribution were well matched between groups. Furthermore, surrogate markers of procedural complexity (screening time and contrast dose) did not differ. Finally, surrogates for total patient ischemic burden, such as total balloon time and angiographically assessed myocardial area at risk (modified APPROACH and Jeopardy scores), were not different, indicating that both groups had a similar amount of myocardium at risk during PCI. The type of stent platform used was not statistically different between groups. Thirteen patients did not have a postprocedural cTnI recorded for administrative reasons or due to patient withdrawal (GLP-1 9 [9%] vs placebo [4%], $P = .25$).

Metabolic changes in a subgroup of 75 patients who underwent additional metabolic assessments at baseline and at PCI are shown in Figure 3. There was no difference in baseline levels of insulin, FFAs, or GLP-1 levels between the 2 groups. Intravenous infusion of GLP-1 increased plasma levels of active GLP-1 to superphysiological levels during the procedure, but there was no significant change in GLP-1 concentration in the placebo group that received saline infusion. A significant rise in FFA levels was seen in both groups compared with baseline levels. Plasma FFA levels have been shown to rise rapidly after administration of heparin, with peak levels rising within 10 minutes of administration.[29] The observed rise was numerically suppressed by the action of GLP-1, consistent with its known action, although this did not reach statistical significance. GLP-1 also produced a substantial rise in plasma insulin levels, whereas these were unchanged in the placebo group. These findings confirm that, when GLP-1 was infused during the procedure, it was present and metabolically active.

Biomarker release

There was no significant difference in the frequency of PMI (the primary end point) between the 2 groups of this study. Overall, the PMI rate was 9.5%, with 8 (9.3%) in the GLP-1–treated arm compared with 9 (9.8%) in the placebo arm ($P = 1.0$). This result is displayed in Figure 3 alongside the other biomarker end points. There was no difference in median cTnI rise between arms (GLP-1 20 [0-58.5] vs placebo 9.5 [0-88.5] ng/L, $P = .25$). Six-hour CKMB was measured in 147 (76.6%) patients (GLP-1 72 vs placebo 75, $P = .74$). There was also no significant difference in CKMB at 6 hours postprocedure (GLP-1 19 [15.75-25] vs placebo 21 [17-27] U/L, $P = .32$). A conditional power calculation demonstrated that even with an increased sample size, the data indicated that it was highly unlikely that the trial would show anything other than a negative result. Given this, the trial was stopped early after the data and safety monitoring committee recommended to the trial

Figure 1



CONSORT diagram.CONSORT diagram for the GOLD PCI trial.

steering committee that the trial was statistically futile to continue.

A number of patients had a change in PCI strategy after randomization, which resulted in them not receiving a stent. The reasons for this are included in Figure 1. A post hoc per-protocol analysis excluding these patients showed no difference in the rate of PMI (GLP-1 8 [10.1%] vs placebo 9 [10.8%], $P = 1.0$) or cTnI rise (GLP-1 22.5 [1.25-89.75] vs placebo 16 [0-60], $P = .38$). The overall study population included 19 patients with diabetes; no PMI events were recorded in either group for these patients, and there was no difference in cTnI rise (GLP-1 6 [0-40.5] vs placebo 16 [0-27], $P = .83$).

Other end points

The remaining secondary end points are recorded in Table III. Very few procedures perturbed TIMI coronary flow score or TIMI myocardial blush grade, and therefore, no difference between the 2 arms was seen. Chest pain score during the procedure was not different between groups, nor were there any differences in the frequency of ST-segment deviation.

Median follow-up was 373 days with good trial retention, as 190 (98.9%) patients were followed up at the planned 12-month telephone consultation. Overall, the 12-month MACCE rate was low, with no cardiovascular mortality in either group. Only 1 death was recorded, as a result of pancreatic cancer, in the

Table I. Demographic data for patients randomized into trial

	GLP-1	Placebo	*P* value
Age, mean ± SD	69.0 ± 9.5	67.1 ± 8.2	.13
Male sex, n (%)	76 (79.2)	76 (79.2)	1.0
Previous MI, n (%)	60 (62.5)	65 (67.7)	.55
Hypertension, n (%)	42 (43.8)	40 (41.7)	.88
Heart failure (EF ≪40%), n (%)	0 (0)	2 (2.1)	.50
Smoking history, n (%)	53 (55.2)	60 (62.5)	.38
Diabetes mellitus, n (%)	9 (9.4)	10 (10.4)	1.0
Metformin use	7 (78)	5 (50)	.44
Body mass index, median [IQR]	28.4 [25.5-31.1]	28.0 [25.5-30.1]	.32
Hemoglobin (g/dL), median [IQR]	14.2 [13.1-14.8]	13.8 [12.9-14.6]	.29
Urea (mmol/L), median [IQR]	5.90 [5.10-7.85]	5.95 [5.18-7.03]	.49
Creatinine (mg/dL)	0.97 [0.86-1.11]	0.94 [0.80-1.05]	.15
Medication use			
β-Blockers, n (%)	68 (70.8)	63 (65.6)	.44
ACEi or ARBs, n (%)	58 (60.4)	53 (55.2)	.56
Statin, n (%)	87 (90.6)	87 (90.6)	1.0
Oral nitrate, n (%)	63 (65.6)	67 (69.8)	.64
Aspirin, n (%)	85 (88.5)	86 (89.6)	.82
Clopidogrel, n (%)	28 (29.2)	32 (33.3)	.53
Ticagrelor, n (%)	18 (18.8)	13 (13.5)	.33
Metformin, n (%*)	7 (78)	5 (50)	.44

MI - myocardial infarction; EF - ejection fraction; ACEi - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker.
* Percentage of diabetic patients only.

placebo group. There was no significant difference in the MACCE rate between groups at 12 months. Figure 4 shows Kaplan-Meier survival analysis for both groups.

Glycemic effects of GLP-1

Plasma glucose concentration measured at baseline and at the time of PCI is illustrated in Figure 2. There was a significant fall in glucose in the GLP-1 arm but no change in the placebo arm. The change in glucose concentration was significantly different between arms (−12.6 [−22.6 to −0.27] vs −3.6 [−9.0 to +5.4] mg/dL, $P \ll .001$). Further glucose measurements were also performed throughout the remaining infusion time as a safety measure: there was an excess of hypoglycemic episodes (plasma glucose ≪70 mg/dL) in the GLP-1 arm (20 [20.8%] vs 2 [2.1%], $P \ll .001$) after PCI. No episodes of hypoglycemia led to symptoms, and in only 1 case was a plasma glucose below 55 mg/dL that required oral glucose administration.

Discussion

Infusion of GLP-1 during elective PCI did not affect the rate of PMI or biomarker rise at 6 hours compared with placebo in this randomized trial, although the observed rate of PMI was lower than expected. No change was seen in TIMI coronary flow score, TIMI myocardial blush

Table II. Procedural data

	GLP-1	Placebo	*P* value
Lesion location, n (%)			.36
LAD*	36 (38.3)	44 (46.8)	
RCA	27 (28.7)	20 (21.3)	
LCx†	19 (20.2)	17 (18.1)	
LMS	4 (4.3)	0 (0)	
Ramus intermedius	1 (1.1)	3 (3.2)	
Multivessel	7 (7.4)	10 (10.6)	
Lesion complexity (B2/C), n (%)	66 (70.2)	69 (73.4)	.75
Quantitative coronary angiography			
Lesion length, mm	20.5 [12.0-31.75]	24.0 [16.0-33.25]	.23
Reference vessel diameter, mm	2.90 [2.63-3.40]	2.96 [2.45-3.27]	.35
Minimal lumen area, mm	0.90 [0.55-1.11]	0.80 [0.42-1.18]	.87
Stenosis (area), %	88.0 [79.75-94.0]	89.0 [82.75-96.1]	.15
Residual stenosis (area), %	7.0 [0.0-17.0]	9.8 [0.0-18.25]	.23
Myocardial area at risk	26.0 [18.5-43.7]	27.75 [18.5-41.3]	.60
Mod. Jeopardy score ≫6, n (%)	8 (8.9)	10 (10.8)	.86
Rentrop score ≫1, n (%)	6 (6.6)	9 (9.7)	.62
Screening time, s	11.1 [7.4-16.4]	10.1 [7.1-14.1]	.35
Contrast dose, mL	160 [130-200]	160 [130-217.5]	.21
Number of stents, n (%)			.91
0 stent‡	14 (14.6)	11 (11.5)	
1 stent	55 (57.3)	57 (59.4)	
2 stents	19 (19.8)	20 (20.8)	
≫3 stents	8 (8.3)	8 (8.3)	
Stent type, n (%)			.21
drug-eluting stent	79 (82.3)	84 (87.5)	
Bare metal stent	4 (4.2)	1 (1.0)	
Average stent diameter, mm	3.0 [2.75-3.50]	3.0 [2.50-3.50]	.28
Total stent length, mm	36 [27-48]	35 [24-56]	.97
Predilation strategy	80 (83.3)	82 (85.4)	.69
Predilation time, s	24 [15-57.5]	28.5 [16.25-49.75]	.78
Postdilation strategy	67 (69.8)	66 (68.8)	.88
Postdilation time, s	31.5 [0-57]	27.5 [0-55]	.59
Total balloon time, s	108 [67.5-145.8]	94 [70-135.75]	.31
Clinical state before implantation			
SBP, mm Hg	139 ± 21	136 ± 21	.28
DBP, mm Hg	76 ± 13	76 ± 12	.99
HR, beat/min	60 [57-72]	62 [58-70]	.57
RPP, beat/min.mm Hg	8500 [7560-9717]	8556 [7560-9520]	.84
Clinical state during implantation			
SBP, mm Hg	137 ± 26	135 ± 24	.54
DBP, mm Hg	67 ± 12	68 ± 11	.64
HR, beat/min	66 [57-71]	64 [59-69]	.47
RPP, beat/min.mm Hg	8766 [7326-10,216]	8585 [7232-10,400]	.83

LAD - left anterior descending artery; RCA - right coronary artery; LCx - left circumflex artery; LMS - left main stem artery; SBP - systolic blood pressure; DBP - diastolic blood pressure; HR - heart rate; RPP - rate pressure product.
* Includes diagonal branches.
† Includes obtuse marginal branches.
‡ Two patients in each group received drug-coated balloons without stenting for in-stent restenosis. None of these patients met the primary end point of PMI.

Table III. Secondary end points

	GLP-1	Placebo	*P* value
Chest pain score	3 [0-5]	2 [0-5.25]	.56
ST-segment deviation ≥1 mm, n (%)	38 (42.7)	31 (35.2)	.39
TIMI coronary flow score = 3, n (%)	92 (98.9)	91 (97.8)	1
TIMI myocardial blush score = 3, n (%)*	89 (97.8)	88 (97.8)	1
MACCE events, n (%)	7 (7.3)	9 (9.4)	.61

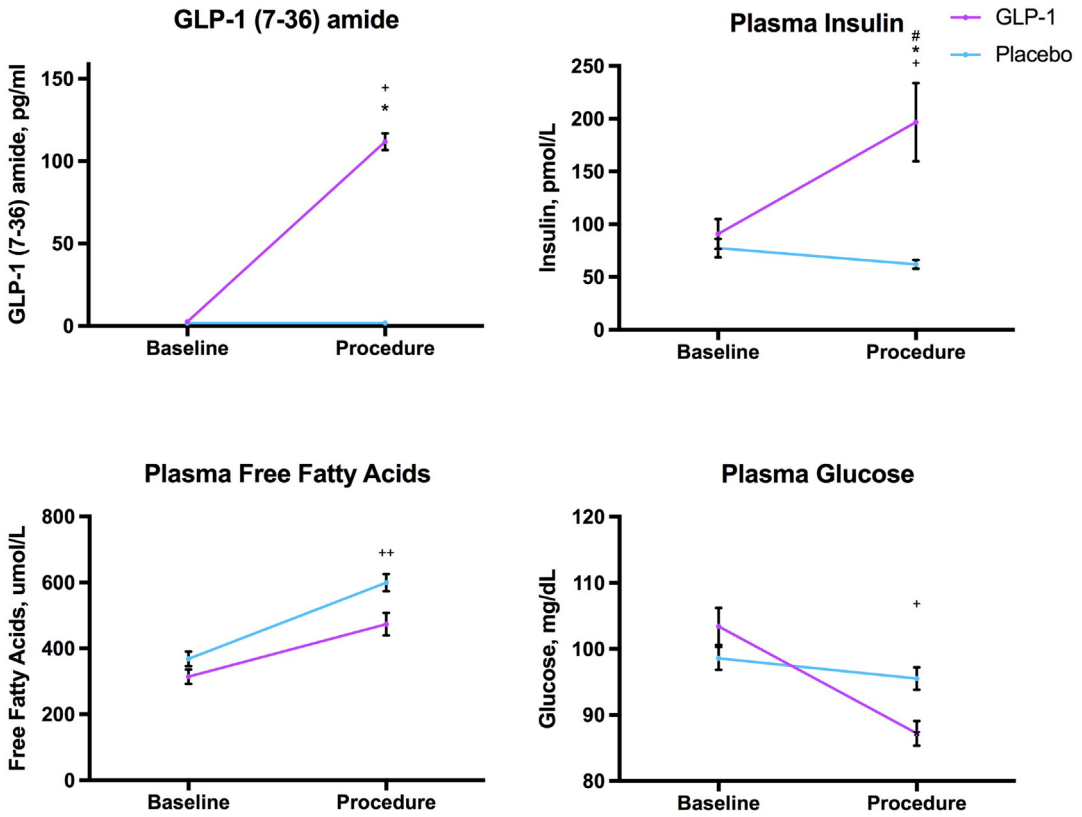
* For patients with a TIMI coronary flow score of 3.

grade, chest pain score, or ST-segment deviation during balloon occlusion. Rates of MACCE and mortality were also low with no difference observed between arms of the study. Plasma GLP-1 levels were increased to supraphysiological levels, that is, more than 50 times greater than basal levels. GLP-1 increased plasma insulin levels and reduced plasma glucose in fasting individuals in expected fashion but was associated with increased episodes of mild asymptomatic hypoglycemia.

GLP-1 has shown promise as a cardioprotective agent, with similar plasma concentrations to this study, reducing left ventricular stunning and cumulative nonlethal ischemic dysfunction during elective PCI, even after only short periods of coronary balloon occlusion,[19-21] GLP-1 receptor agonists have improved the myocardial salvage index when administered during ST-elevation myocardial infarction.[18] Finally, a number of cardiovascular outcome studies have demonstrated improved outcomes when GLP-1 receptors have been used to treat diabetes.[14,30] Because cTnI rise is associated with cardiomyocyte necrosis, the lack of improvement compared with placebo in this trial shows that there was no protective effect against lethal IR injury observed when assessed by cardiac biomarkers.[31] The study clearly demonstrated this with groups well matched for demographic and procedural characteristics and, importantly, surrogates of myocardial area at risk.

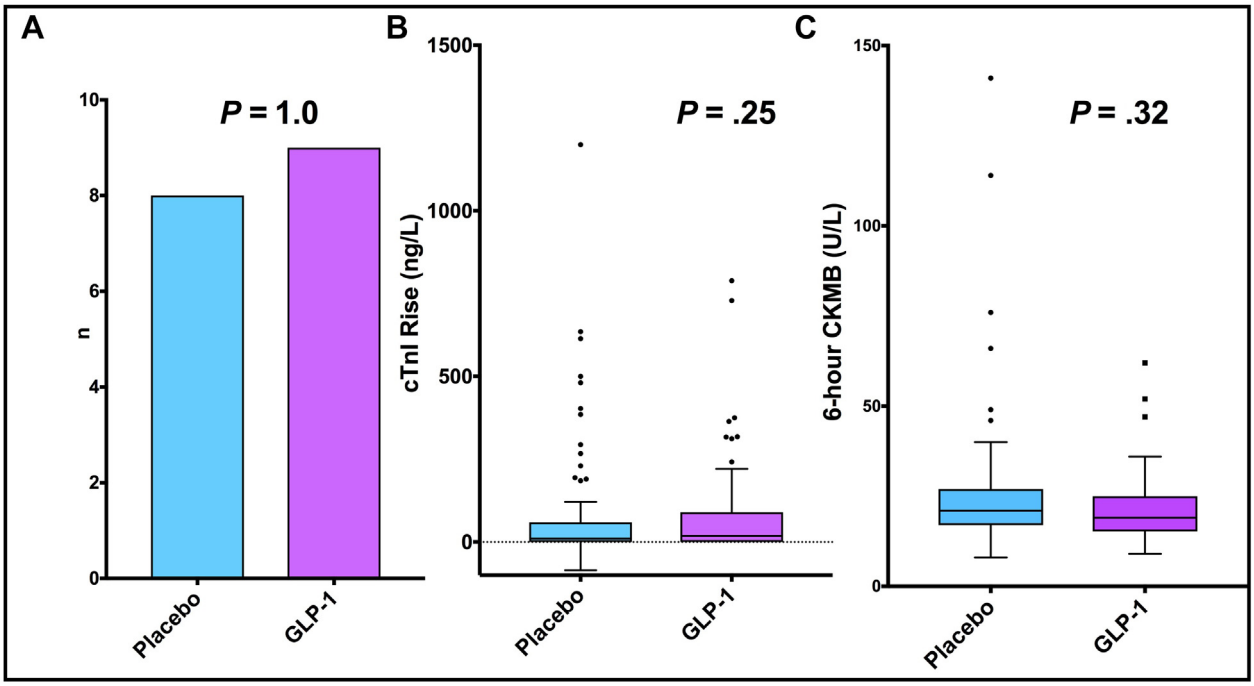
The location of the GLP-1 receptor within the human myocardium remains controversial, but recently, its presence in the ventricle has been confirmed.[32-34] The beneficial effect of GLP-1 on myocardial performance during ischemia may be mediated directly via receptors on the cardiomyocyte or through indirect paracrine

Figure 2



Metabolic bloods.Comparison of plasma levels of GLP-1 (7-36) amide, insulin, and FFAs (in the metabolic subgroup), and plasma glucose in all patients (mean ± SEM). *$P \ll .001$ between change in GLP-1 and placebo during study, +$P \ll .001$ between GLP-1 baseline and procedure, ++$P \ll .05$ between both groups baseline and procedure, #$P \ll .001$ between placebo baseline and procedure.

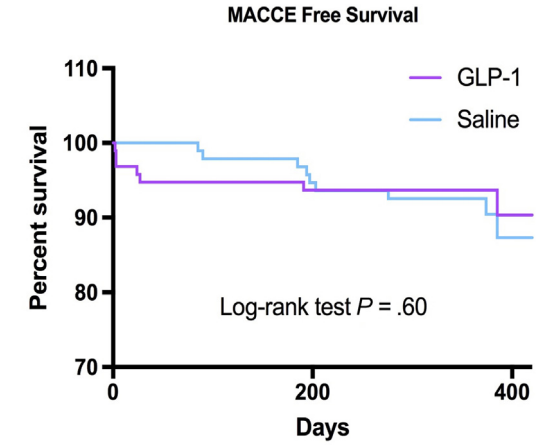
Figure 3



Biomarker end points for GOLD-PCI trial.**A**, The number of primary end points (PMI) in each group. **B**, The change in cTnI at 6 hours postprocedure. **C**, The 6-hour CKMB level.

effects, perhaps via the adenosine receptor changing increasing coronary perfusion.[33,35] Because the mechanism of PMI is microembolism, prolonged balloon inflation, and release of vasoactive plaque constituents into the coronary microcirculation, our study cannot confirm that GLP-1 does not protect against spontaneous

Figure 4



Major adverse cardiovascular and cerebrovascular events.Kaplan-Meier survival analysis for 12-month follow-up of MACCE (all-cause death, MI, hospitalization for heart failure, or unstable angina).

myocardial infarction following plaque rupture and thrombotic occlusion of the coronary arteries. However, we believe that the study does provide some evidence against this hypothesis. Furthermore, although our study has shown that GLP-1 does not protect against lethal IR injury in the elective PCI setting, there may still be clinical utility for an agent that reduces ischemic dysfunction and myocardial stunning. In a pilot study of patients with acute myocardial infarction and impaired left ventricular systolic function, GLP-1 improved ejection fraction.[23] Our data suggest that this is due to protection against nonlethal stunning and ischemic dysfunction rather than reduced infarct size. This is supported by other studies investigating the use of GLP-1 to control plasma glucose in critically ill surgical patients that noted reduced inotropic or vasopressor requirements.[36,37] GLP-1 may therefore still potentially have a therapeutic role in patients suffering from cardiogenic shock.

The metabolic effect of GLP-1 in fasting patients, predominantly without diabetes, increased plasma insulin and decreased plasma glucose concentrations, resulting in an increased frequency of hypoglycemic episodes. GLP-1 is thought to be glucose dependent and inactive when plasma glucose falls below 70 mg/dL.[13,38,39] Our finding is consistent with observations in some other studies that hypoglycemic events were more frequent following prolonged GLP-1 infusion in patients with cardiovascular disease.[40,41] It is noteworthy that early pharmacokinetic studies into the action of GLP-1 investigated young, healthy males rather than the real-world population of this study. Although all episodes of hypoglycemia were asymptomatic, this finding suggests that careful glucose monitoring is needed in studies using GLP-1, particularly if administered to fasting, nondiabetic patients.

Limitations

Our study had a lower event rate than anticipated and was terminated early for reasons of futility. However, statistical modeling confirmed that, despite this, the study was negative. Recruiting more patients would not have changed the outcome of the study. The low event rate probably reflects improvement in modern PCI technique and equipment but may also reflect a lower-risk study population recruited compared with previous studies. Patients with diabetes were underrecruited, as several therapies for diabetes were exclusion criteria for the study. Female patients and those with low body mass index are at higher risk of PMI, and these groups were underrepresented in the study population.[42] Furthermore, there were small numbers of patients undergoing multivessel PCI or treatment of chronic total occlusions, and no patients undergoing rotational atherectomy, which are more likely to sustain microembolic injury and PMI. It is possible that those patients with a greater risk of ischemic may benefit from GLP-1 treatment. This work remains to be undertaken. All patients in this study routinely received nitrates, and frequently opiates, and these could have contributed to a conditioning effect on the myocardium in both groups.[8] The authors acknowledge that the fourth universal definition of myocardial infarction requires clinical, angiographic, ECG, or imaging support for the diagnosis of PMI in addition to biomarker rise.[43] These changes are important for a clinical diagnosis, although including these in the primary end point would have further reduced the power of the study. The authors also note that the number of patients not receiving a PCI also reduced the power of the study, although, as discussed above, additional participants would not have altered the result.

The pragmatic choice of 6-hour cTnI measurement due to a high number of day-case procedures may have resulted in a reduced rate of PMI detection, as the peak cTnI could have occurred at a time point after the blood was sampled. The absence of a nonsignificant trend between the groups makes it improbable that sampling at a later time point would alter the trial result. Furthermore, CK-MB, which has earlier release kinetics, was low and similar between groups, which are highly suggestive that an effect had not been missed through early biomarker sampling.[44] Hypoglycemia may be associated with myocardial injury. The authors note that there was mild hypoglycemia in a number of patients in the GLP-1 group. However, as this was mild, transient, and rapidly treated, it is unlikely to affect the primary outcome.

Conclusion

In this randomized, double-blind, placebo-controlled trial, GLP-1 infusion at 1.2 pmol/kg/min was safely administered during elective PCI but was not associated with a reduction in the rate of PMI or cardiac biomarker release at 6 hours postprocedure.

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