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CLINICAL RESEARCH
Acute coronary syndromes

Glucagon-like peptide 1 levels predict cardiovascular risk in patients with acute myocardial infarction

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Aims Glucagon-like peptide 1 (GLP-1) is a gut incretin hormone inducing post-prandial insulin secretion. Glucagon-like peptide 1 levels were recently found to be increased in patients with acute myocardial infarction. Glucagon-like peptide 1 receptor agonists improve cardiovascular outcomes in patients with diabetes. The aim of this study was to assess the predictive capacity of GLP-1 serum levels for cardiovascular outcome in patients with myocardial infarction.

Methods and results In 918 patients presenting with myocardial infarction [321 ST-segment elevation myocardial infarction and 597 non-ST-segment elevation myocardial infarction (NSTEMI)] total GLP-1, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the Global Registry of Acute Coronary Events (GRACE) score were assessed at time of hospital admission. The primary composite outcome of the study was the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Kaplan–Meier survival plots and univariable Cox regression analyses found GLP-1 to be associated with adverse outcome [hazard ratio (HR) of logarithmized GLP-1 values: 6.29, 95% confidence interval (CI): 2.67–14.81; $P < 0.0001$]. After further adjustment for age, sex, family history of cardiovascular disease, smoking, diabetes, hypertension, hypercholesterinaemia, glomerular filtration rate (GFR) CKD-EPI, hs-CRP, hs-Troponin T, and NT-proBNP levels the HR remained significant at 10.98 (95% CI: 2.63–45.90; $P = 0.0010$). Time-dependent receiver operating characteristic curve analyses illustrated that GLP-1 levels are a strong indicator for early events. For events up to 30 days after admission, GLP-1 proved to be superior to other biomarkers including hs-Troponin T, GFR CKD-EPI, hs-CRP, and NT-proBNP. Adjustment of the GRACE risk estimate by addition of GLP-1 increased the area under the receiver operating characteristic curve over time in NSTEMI patients.

Conclusion In patients hospitalized for myocardial infarction, GLP-1 levels are associated with cardiovascular events.

Keywords Incretin • GLP-1 • Cardiovascular risk • Mortality • Myocardial infarction

Introduction

Based on current guidelines early risk stratification in patients with acute myocardial infarction is essential to identify patients requiring immediate or early coronary angiography.[1] While patients with STEMI (ST-segment elevation myocardial infarction) require immediate revascularization, patients with NSTEMI (non-ST-segment elevation myocardial infarction) can be stratified by symptoms and

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comorbidities to receive coronary angiography within 24 or 72 h. Currently, validated scoring systems, such as the Global Registry of Acute Coronary Events (GRACE) score and the TIMI risk score are used to assess the patient's individual risk and determine triage and therapeutical decisions.[2,3]

Glucagon-like peptide 1 (GLP-1) is an incretin hormone, that is secreted from gut enteroendocrine L-cells following food intake leading to insulin secretion in a glucose-dependent manner.[4] This mode of action has made GLP-1 an attractive therapeutic target for the treatment of diabetes.[5] Experimental studies found GLP-1 to exert pleiotropic vascular- and cardioprotective effects beyond its glucoregulatory function.[4] Importantly, four large clinical trials could show that treatment with GLP-1 receptor agonists reduce cardiovascular events in high-risk patients with diabetes.[6–9] Recently, we found endogenous circulating GLP-1 concentrations to be elevated in patients with acute myocardial infarction and increased GLP-1 secretion in mice following experimental permanent LAD ligation, which occurred independent of food intake.[10] Increased GLP-1 secretion in response to myocardial infarction proved to be cardioprotective in mice by augmenting left ventricular contractility.[10] These findings identified GLP-1 as an endogenous counter-regulatory cardioprotective peptide during myocardial infarction. In this study, we sought to assess the predictive capacity of an activated GLP-1 system for cardiovascular outcome in patients with myocardial infarction.

Methods

Study population and follow-up

Between 2006 and 2010, we recruited 918 patients [mean age ± standard deviation (SD) = 67 ± 13 years; men 73%] with STEMI (35%) or NSTEMI (65%) at the time of hospital admission at the University Hospital Heidelberg. The only exclusion criterion was refusal to provide written informed consent. Patient risk stratification, treatment, and management decisions were left to the discretion of the attending cardiologist. When a patient reported another hospital admission for cardiovascular reasons during the study interval, hospital discharge reports were obtained and checked for a diagnosis of a cardiovascular event or death. In this study, we included both patients with completed follow-up and also patients who were lost to follow-up and who were treated as censored observations in the Cox regression model. The study follow-up was performed by using hospital records, questionnaires, phone calls, and death certificates. The study complies with the Declaration of Helsinki and the locally appointed ethics committee approved the research protocol. All patients provided written informed consent. The GRACE risk score has been described elsewhere.[3] Briefly, the GRACE score is derived from eight variables that are available at hospital admission (age, heart rate, systolic blood pressure, serum creatinine concentration, Killip class, cardiac arrest, presence of ST-segment deviation, and elevated cardiac enzymes/markers). At the moment of hospital admission, the respective values for these variables were entered into the GRACE risk calculator (available at http://www.outcomes-umassmed.org/grace).

Laboratory parameters

All blood samples were drawn in the chest pain unit (CPU) before medical treatment was initiated in the CPU and prior angiography. Serum samples were obtained by venipuncture at the time of admission and stored at -80°C. High-sensitivity Troponin T was measured in all patients using the COBAS E411 platform (Roche Diagnostics). For patients that presented between 2006 and 2008, the fourth generation Troponin T assay (Roche Diagnostics) was determined during clinical routine. A cut-off of 0,03 ng/mL was considered as indicative of myocardial injury in all patients. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured by an immunoassay on an Elecsys 2010 instrument (Roche Diagnostics). Total GLP-1 levels were determined by using a commercial ELISA kit (Millipore). Readjudication of the diagnosis of myocardial infarction and type was performed by two independent cardiologists based on all available clinical data including angiography and imaging (echocardiography, magnetic resonance imaging if available). This study is based on a retrospective analysis from frozen serum samples. Additional clinical characteristics/parameters were also assessed retrospectively from the routine clinical documentation system.

Statistical analysis

Continuous data are presented as mean ± SD or median (Q1–Q3) in case of skewed data. Categorical outcomes are given as absolute and relative frequencies (%). For descriptive purposes, baseline characteristics and Kaplan–Meier curves are shown in dependence of the empirical GLP-1 tertiles (low: GLP-1 < 35.5 pM, medium: GLP-1 between 35.5 and 53.5 pM, and high: GLP-1 > 53.5 pM). All further analyses refer to the continuously measured GLP-1 levels at admission.

The association between baseline characteristics and GLP-1 tertiles was assessed using the Cochrane–Armitage test for nominal characteristics and using the Spearman correlation coefficient ρ in the case of continuous characteristics. Kaplan–Meier cumulative event curves were used to display survival outcomes in dependence of GLP-1 tertiles. Differences between the GLP-1 tertiles were investigated using a Cox regression model. Median follow-up times were computed separately for the combined triple endpoint and all-cause mortality by the reverse Kaplan–Meier method. Univariable and multivariable Cox regression models were applied to investigate the association of logarithmized GLP-1 levels and survival outcomes. Skewed data were logarithmically transformed to improve model stability. The proportional hazards assumption was checked graphically using Schoenfeld residuals. If necessary, the Cox regression models included a logarithmic interaction term of logarithmized GLP-1 values with time. The reported hazard ratios of the logarithmized GLP-1 values refer to the hazard ratio at 0 days. Time-dependent ROC curves were estimated to investigate the ability of GLP-1 levels to predict future outcomes. The performance of GLP-1 in the entire collective was compared to other clinically relevant markers [glomerular filtration rate (GFR) CKD-EPI, hs-Troponin T, NT-proBNP, and hs-CRP) by means of the area under the receiver operating characteristic curve (AUC). In the subgroup of NSTEMI patients, we analysed the ability of the GRACE score alone and in combination with NT-proBNP and GLP-1 to predict cardiovascular outcomes. All time-dependent ROC curves were estimated using the inverse probability of censoring weighting method by Hajime Uno *et al.*[11] The level of significance was set at 5%. No adjustments were made for multiple comparisons. Statistical analyses were performed using SAS software version 9.4 (PROC PHREG; SAS Institute, Cary, NC, USA) and R, version 3.5.1,[12] packages timeROC[13] and survival.[14]

Results

Baseline characteristics

Clinical and laboratory baseline characteristics, biomarker concentrations and baseline medication according to GLP-1 tertiles are shown in *Tables 1* and *2*. GLP-1 tertiles were significantly associated with various cardiovascular risk factors including smoking, pre-existing

Table 1 Baseline characteristics

Characteristics	All patients ($n = 918$)	Tertiles of GLP-1 (pM) <35.5 ($n = 301$)	35.5–53.5 ($n = 299$)	>53.5 ($n = 299$)	*P*-value[a]
Demographics					
Age (years)	66.9 ± 12.7	64.9 ± 13.3	67.3 ± 11.9	68.6 ± 12.8	0.0001
Sex (male)	672 (73.2%)	192 (63.8%)	232 (77.6%)	235 (78.6%)	<0.0001
Cardiovascular risk factors					
Smoker	498 (59.4%)	188 (66.7%)	145 (53.7%)	152 (56.5%)	0.0141
Hypertension	664 (75.4%)	206 (71.5%)	216 (76.3%)	229 (78.7%)	0.0451
Hypercholesterolaemia	452 (58.2%)	136 (53.5%)	150 (58.1%)	161 (63.9%)	0.0182
Diabetes mellitus	223 (25.4%)	50 (17.2%)	72 (25.4%)	98 (34.5%)	<0.0001
Systolic blood pressure (mmHg)	143.8 ± 23.2	145.8 ± 24.4	143.6 ± 22.8	141.8 ± 22.2	0.1325
Kidney disease	101 (11.2%)	22 (7.3%)	27 (9.0%)	52 (17.5%)	<0.0001
Liver disease	17 (1.9%)	4 (1.3%)	5 (1.7%)	8 (2.7%)	0.2239
COPD	76 (8.4%)	26 (8.6%)	23 (7.7%)	27 (9.1%)	0.8540
Atrial fibrillation	74 (8.2%)	20 (6.6%)	15 (5.0%)	39 (13.1%)	0.0042
GRACE score	149.1 ± 31.2	142.7 ± 30.2	149.5 ± 30.2	154.9 ± 32.2	<0.0001
GRACE category					
Low (≤108)	67 (7.3%)	34 (11.3%)	17 (5.7%)	16 (5.4%)	
Medium (108–140)	314 (34.2%)	111 (36.9%)	107 (35.8%)	89 (29.8%)	
High (>140)	537 (58.5%)	156 (51.8%)	175 (58.5%)	194 (64.9%)	
Previous cardiovascular disease					
Family history of CVD	305 (40.2%)	105 (40.7%)	96 (38.7%)	97 (40.9%)	0.9691
Myocardial infarction	218 (24.9%)	71 (24.4%)	64 (22.6%)	79 (27.8%)	0.3475
PTCA	244 (27.9%)	74 (25.5%)	84 (29.4%)	83 (29.8%)	0.2595
CABG	92 (10.4%)	21 (7.1%)	36 (12.5%)	34 (11.9%)	0.0587
Myocardial infarction subtype					
NSTEMI	597 (65.0%)	207 (68.8%)	198 (66.2%)	187 (62.5%)	0.1077
STEMI	321 (35.0%)	94 (31.2%)	101 (33.8%)	112 (37.5%)	
Risk markers at baseline					
hs-Troponin T (ng/L)	146.3 (46.45–492.6)	107.3 (42.97–371.65)	160.5 (46.11–504.7)	180.1 (51.5–615.7)	0.0134
NT-proBNP (pg/mL)	663.6 (184.5–2271)	401.1 (137.6–1512)	662.6 (171.9–2051)	1149.5 (293.5–3908)	<0.0001
hs-CRP (mg/L)	4.28 (1.70–15.26)	3.39 (1.37–9.19)	3.91 (1.67–12.51)	6.88 (2.37–33.9)	<0.0001
Serum creatine kinase (U/L)	181 (107–398)	161 (101–325)	191 (113–437)	210 (110–419)	0.0316
Glucose (mg/dL)	129 (108–158)	121 (105–150)	129 (107–156)	136 (117–180)	<0.0001
GFR CKD-EPI (mL/min/1.73 m^2)	75.8 ± 24.6	82.8 ± 21.8	77.2 ± 22.0	66.9 ± 26.9	<0.0001

Continuous variables are expressed as mean ± SD or median (Q1–Q3) in case of skewed data. Categorical variables are shown as absolute and relative frequencies.
[a]*P*-value of the test that Spearman's rank correlation coefficient $\rho \neq 0$ in the case of continuous characteristics or *P*-value of the Cochrane–Armitage test in the case of nominal characteristics.

hypertension, hypercholesterolaemia, and diabetes. Furthermore, GLP-1 tertiles were positively correlated with the GRACE risk score. Most of the patients at the lowest estimated cardiovascular risk based on the GRACE risk score after myocardial infarction (low GRACE score) were in the lowest GLP-1 tertile (<35.5 pM), while the majority of patients at a high GRACE risk score were in the highest GLP-1 tertile (>53.5 pM). GLP-1 tertiles were also positively correlated with kidney dysfunction and markers of ongoing ischaemia and necrosis, myocardial dysfunction, and inflammation, as indicated by the levels of GFR CKD-EPI, serum creatine kinase (CK), hs-Troponin T, NT-proBNP, and hs-CRP. GLP-1 tertiles were not associated with previous myocardial infarction or family history of cardiovascular disease (*Table 1*).

Glucagon-like peptide 1 levels and cardiovascular risk

Among the 918 patients enrolled in the study a combined endpoint of the first occurrence of non-fatal myocardial infarction or non-fatal stroke or cardiovascular death (3-P MACE) was observed in 62 patients (7%) (29 patients with non-fatal myocardial infarction, four patients with non-fatal stroke, and 29 patients with cardiovascular death), while death (all-cause mortality) was observed in 68 patients (7%) (*Tables 3* and *4*). The median follow-up was 310 days for the combined triple endpoint and 311 days for all-cause mortality. Increasing GLP-1 tertiles predicted a significant increased risk for the combined triple endpoint of non-fatal myocardial infarction, non-fatal

Table 2 Baseline medication

Premedication	All patients ($n = 697$)[a]	Tertiles of GLP-1 (pM) <35.5 ($n = 237$)[a]	35.5–53.5 ($n = 225$)[a]	>53.5 ($n = 223$)[a]	*P*-value[b]
ACEi/ARB	333 (49.1%)	95 (41.3%)	110 (50.5%)	123 (56.4%)	0.0013
MRA	26 (3.9%)	6 (2.6%)	6 (2.8%)	14 (6.5%)	0.0386
Calcium channel blocker	121 (17.9%)	35 (15.2%)	37 (17.0%)	47 (21.6%)	0.0810
Beta-blocker	290 (42.8%)	86 (37.2%)	91 (41.9%)	109 (49.8%)	0.0073
Antiplatelet therapy	277 (39.9%)	82 (34.6%)	99 (44.0%)	95 (42.8%)	0.0698
Phenprocoumon/warfarin	46 (6.7%)	12 (5.1%)	10 (4.5%)	24 (11.0%)	0.0146
Statin	220 (32.0%)	65 (27.7%)	67 (30.2%)	87 (39.7%)	0.0064
Diuretic	209 (30.8%)	55 (23.8%)	64 (29.4%)	89 (40.8%)	0.0001
Antidiabetic premedication					
Metformin	66 (9.6%)	8 (3.4%)	25 (11.2%)	32 (14.6%)	<0.0001
Sulfonylurea/glinides	51 (7.4%)	7 (3.0%)	20 (9.0%)	23 (10.5%)	0.0022
Insulin	56 (8.1%)	16 (6.8%)	16 (7.1%)	24 (10.9%)	0.1153

Data are shown as absolute and relative frequencies.
ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.
[a]No information on medication for 221 patients.
[b]*P*-value of the Cochrane–Armitage test.

Table 3 Univariable Cox regression for glucagon-like peptide 1 tertiles

Survival outcome	No. events	Comparison of GLP-1 tertiles, pM	Estimated hazard ratio (95% CI)[a]	*P*-value
Combined triple endpoint	62	Low, <35.5 vs. medium, 35.5–53.5	5.56 (1.54–20.07)	0.0088
		Low, <35.5 vs. high, >53.5	22.47 (3.20–157.62)	0.0017
		Medium, 35.5–53.5 vs. high, >53.5	4.04 (1.55–10.51)	0.0042
All-cause mortality	68	Low, <35.5 vs. medium, 35.5–53.5	5.10 (1.64–15.88)	0.0049
		Low, <35.5 vs. high, > 53.5	15.23 (2.82–82.42)	0.0016
		Medium, 35.5–53.5 vs. high, >53.5	2.99 (1.29–6.93)	0.0108

Both models include an interaction term between GLP-1 tertile and log(time+1).
[a]Estimated hazard ratio at 0 days.

stroke or cardiovascular death (*Figure 1A* and *Table 3*) and all-cause mortality (*Figure 1B* and *Table 3*).

Univariable Cox regression analyses based on the continuously measured GLP-1 levels revealed that GLP-1 levels at hospital admission predicted the first occurrence of the combined triple endpoint [hazard ratio (HR) of logarithmized GLP-1 values: 6.29; 95% confidence interval (CI): 2.67–14.81; $P < 0.0001$] as well as cardiovascular (HR: 6.74; 95% CI: 2.64–17.21; $P < 0.001$) and overall mortality (HR: 5.71; 95% CI: 2.59–12.60; $P < 0.0001$) (*Table 4*). GLP-1 levels were not significantly predictive for non-fatal myocardial infarction, non-fatal stroke, rehospitalization (for acute coronary syndrome), and coronary reintervention (following previous coronary stent implantation) (*Table 4*).

Multivariable Cox regression analyses based on continuous GLP-1 levels are presented in *Table 5*. Adjustment for age and sex (multivariable Model 1) and further adjustment for smoking, hypertension, hypercholesterolaemia, diabetes, and family history of cardiovascular disease (multivariable Model 2) did not affect the association of GLP-1 with adverse outcomes (*Table 5*). In an additional multivariable Cox regression analysis (multivariable Model 3) we extended model 2 to further adjustment for GFR CKD-EPI, hs-Troponin T, NT-proBNP, and hs-CRP. In this model, the association between GLP-1 and the combined triple endpoint remained significant with a *P*-value of 0.0010 (HR: 10.98; 95% CI: 2.63–45.90), while mortality showed a non-significant trend (HR: 3.58; 95% CI: 0.91–14.04; $P = 0.0675$). Finally, in multivariable Cox regression model 4, we adjusted for all baseline variables from *Table 1* with a *P*-value <0.25 in the univariable Cox regression analysis [(i) *combined triple endpoint:* age, hypertension, hypercholesterolaemia, diabetes mellitus, systolic blood pressure, kidney disease, liver disease, atrial fibrillation, family history of cardiovascular disease, myocardial infarction, PTCA, CABG, myocardial infarction subtype (NSTEMI/STEMI), GFR CKD-EPI and logarithmized values of, NT-proBNP, hs-CRP, and glucose; (ii) *death:* age, hypertension, diabetes mellitus, family history of cardiovascular disease, myocardial infarction, myocardial infarction subtype (NSTEMI/STEMI), GFR CKD-EPI, and logarithmized values of hs-Troponin T,

NT-proBNP, hs-CRP, and glucose]. In this model, GLP-1 was still significantly associated with the first occurrence of the combined triple endpoint and death. Furthermore, adjustment for medication did not affect the significant association between GLP-1 levels and cardiovascular endpoints as shown in Supplementary material online, *Table S1*.

As the Schoenfeld residuals indicated a violation of the proportional hazards assumption for GLP-1, all aforementioned Cox regression models included a logarithmic interaction effect between GLP-1 and time. This interaction term was statistically significant in all models, except for Models 3 and 4 for all-cause mortality and indicated that the hazard ratio of logarithmized GLP-1 values decreases over time.

Table 4 Univariable Cox regression for log(GLP-1)

Survival outcomes	Number of events	Estimated hazard ratio (95% CI)[a]	*P*-value
Combined triple endpoint[b]	62	6.29 (2.67–14.81)	<0.0001
All-cause mortality[b]	68	5.71 (2.59–12.60)	<0.0001
Cardiovascular mortality[b]	29	6.74 (2.64–17.21)	<0.0001
Non-fatal myocardial infarction	29	1.08 (0.53–2.21)	0.8250
Non-fatal stroke	4	1.44 (0.23–8.89)	0.6967
Rehospitalization	217	0.91 (0.70–1.19)	0.4992
Coronary reintervention	91	0.96 (0.63–1.45)	0.8371

[a]Estimated hazard ratio (at 0 days in the presence of an interaction term with time).
[b]Model includes an interaction term between log(GLP-1) and log(time+1).

Consequently, high GLP-1 values are primarily associated with events occurring early after myocardial infarction.

Kaplan–Meier cumulative event curves likewise demonstrated a higher risk for the combined triple endpoint and death in higher GLP-1 tertiles especially at early time points (*Figure 1*). Time-dependent receiver operating characteristic curve analyses illustrated that GLP-1 is a strong indicator for early events (Supplementary material online, *Figures S1* and *S2* and *Tables S2* and *S3*), which proved to be superior to hs-Troponin T, GFR CKD-EPI, NT-proBNP, and hs-CRP within the first month (Supplementary material online, *Figure S1*) and remained superior to hs-CRP and hs-Troponin T overtime for the combined triple endpoint. Adjustment of the GRACE risk estimate by GLP-1 increased the AUC for the combined triple endpoint after 1 month from 0.85 (GRACE) to 0.88 (GRACE + GLP-1) in NSTEMI patients. Addition of GLP-1 to a model containing GRACE and NT-proBNP led to a further improvement in model performance (increase in AUC from 0.87 for GRACE + NT-proBNP to 0.90 for GRACE + NT-proBNP + GLP-1). A similar increase of the AUC after addition of GLP-1 can be observed after 1 week, 2 weeks, and 6 months for the combined triple endpoint (Supplementary material online, *Figure S3*) and for mortality (Supplementary material online, *Figure S4*). Admission GLP-1 levels in patients with myocardial infarction were associated with cardiovascular prognosis in the subgroups of patients with or without diabetes (Supplementary material online, *Figures S5* and *S6* and *Tables S4* and *S5*).

Discussion

This study demonstrates that GLP-1 is a powerful biomarker of cardiovascular events (3-P MACE) and death in patients with acute myocardial infarction. Glucagon-like peptide 1 is a strong indicator

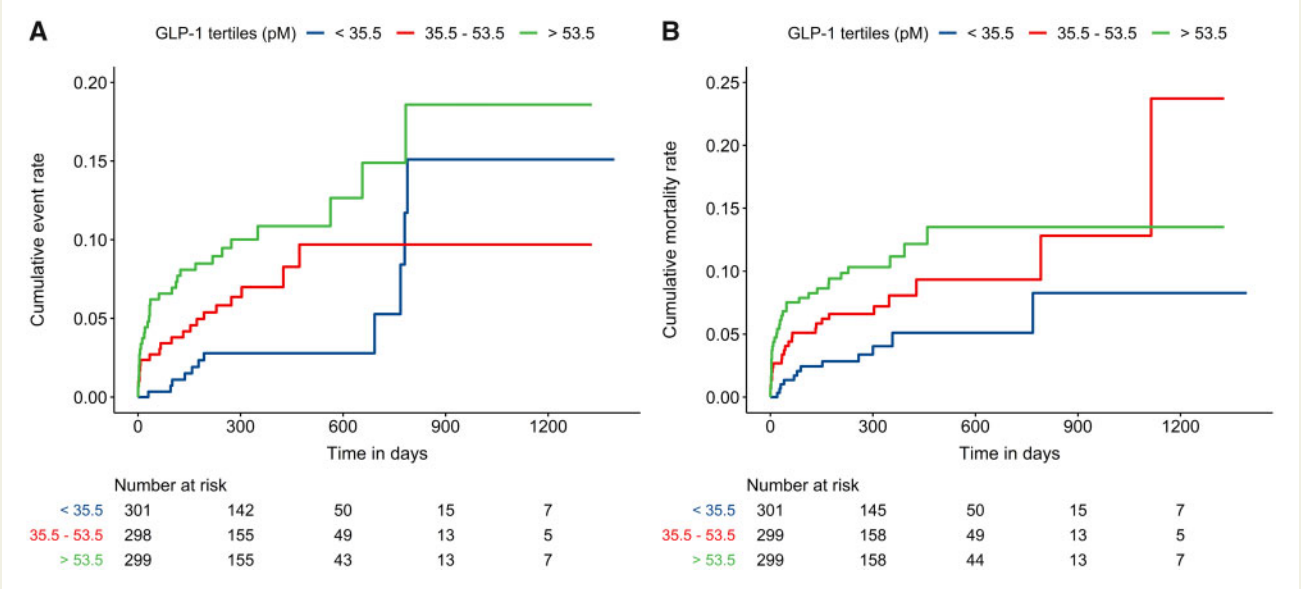

Figure 1 (*A*) Kaplan–Meier cumulative event curves for the combined triple endpoint (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) with patients separated by GLP-1 tertiles. (*B*) Kaplan–Meier cumulative event curves for all-cause mortality with patients separated by GLP-1 tertiles.

Table 5 Multivariable Cox regression for log(GLP-1)

Survival outcome	Model 1		Model 2		Model 3		Model 4	
	Estimated hazard ratio (95% CI)	*P*-value	Estimated hazard ratio (95% CI)	*P*-value	Estimated hazard ratio (95% CI)	*P*-value	Estimated hazard ratio (95% CI)	*P*-value
Combined triple endpoint	5.85 (2.48–13.82)	<0.0001	10.97 (2.89–41.67)	0.0004	10.98 (2.63–45.90)	0.0010	10.36 (2.04–52.70)	0.0048
All-cause mortality	4.98 (2.25–10.99)	<0.0001	5.91 (1.71–20.48)	0.0051	3.58 (0.91–14.04)	0.0675	4.74 (1.47–15.30)	0.0093

All models include an interaction term between log(GLP-1) and log(time + 1). The estimated hazard ratio is the hazard ratio at 0 days. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, smoking, hypertension, hypercholesterolaemia, diabetes mellitus, and family history of cardiovascular disease. Model 3 was adjusted for age, sex, smoking, hypertension, hypercholesterolaemia, diabetes mellitus, family history of cardiovascular disease, GFR CKD-EPI, and logarithmized values of hs-Troponin T, NT-proBNP, and hs-CRP. Model 4 was adjusted for all baseline variables from *Table 1* (except for GRACE-Score and GRACE–Category) with a *P*-value <0.25 in the univariable Cox regression analysis. For the combined triple endpoint, these were age, hypertension, hypercholesterolaemia, diabetes mellitus, systolic blood pressure, kidney disease, liver disease, atrial fibrillation, family history of cardiovascular disease, myocardial infarction, PTCA, CABG, myocardial infarction subtype (NSTEMI/STEMI), GFR CKD-EPI, and logarithmized values of NT-proBNP, hs-CRP, and glucose. For all-cause mortality, these were age, hypertension, diabetes mellitus, family history of cardiovascular disease, myocardial infarction, myocardial infarction subtype (NSTEMI/STEMI), GFR CKD-EPI, and logarithmized values of hs-Troponin T, NT-proBNP, hs-CRP, and glucose.

especially for early events for which it proved to be superior to established biomarkers like hs-CRP, hs-Troponin T, NT-proBNP, and GFR CKD-EPI. Further adjustment for age, sex, cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes mellitus, and family history of cardiovascular disease), and well-established risk indicators (GFR CKD-EPI, hs-Troponin, NT-proBNP and hs-CRP) did not affect this significant association.

In a previous experimental study, we found the GLP-1 system to be activated during myocardial infarction in mice leading to augmented left ventricular contractility.[10] Importantly, clinical studies found treatment with the GLP-1 receptor agonist exenatide at the time of primary percutaneous coronary intervention to reduce infarct size and improve left ventricular function in patients with myocardial infarction.[15–17] Furthermore, four large clinical outcome trials could show that activation of the GLP-1 system reduced cardiovascular events in patients with diabetes at high cardiovascular risk.[6–9]

We have earlier reported higher GLP-1 levels to be present in patients with STEMI compared to clinically stable patients with the angiographic exclusion of coronary artery disease.[10] Since myocardial infarction is known to induce a massive systemic inflammatory activation with the release of multiple proinflammatory mediators,[18–20] we measured circulating cytokines in STEMI patients after admission. Interestingly, GLP-1 strongly correlated with cytokines like IL-6 in these STEMI patients.[10] This is in line with previous experimental work showing that inflammatory stimuli like LPS and IL-1β directly induce GLP-1 secretion by an IL-6 dependent mechanism.[21,22] Consistently, GLP-1 levels in patients with sepsis are strongly elevated compared to patients without sepsis and were positively correlated with inflammatory markers like IL-6 and CRP.[22,23] In this study, endogenous GLP-1 levels of patients with acute myocardial infarction were positively associated with the inflammatory parameter hs-CRP levels (*Table 1*). On the basis of these findings, we assume that the inflammatory response after myocardial infarction leading to elevation of proinflammatory cytokines directly induces GLP-1 secretion in patients with STEMI/NSTEMI. Although the cross-sectional design of the study does not imply causality, we hypothesize that patients with the highest GLP-1 secretion had the strongest systemic inflammatory response following myocardial ischaemia, and therefore, the worst prognosis. We assume that the massive systemic inflammatory activation causes the association between high GLP-1 levels and adverse outcome, while GLP-1 might still be protective.

As shown in *Figure 1*, Supplementary material online, *Figures S1* and *S2* higher GLP-1 levels strongly correlate with adverse outcome only at early timepoints. After 600 days, clear separation of the 3 GLP-1 tertiles was lost (*Figure 1*), which might be explained by the limited number of patients at risk at this time point. Future studies with more patients and repeated GLP-1 measurements over time are necessary to better understand this observation.

Considering the broad cardiovascular protective effects of GLP-1 it appears unlikely that higher GLP-1 levels after myocardial infarction in the current study are detrimental and responsible for adverse outcomes and early death. Previous experimental work showed that the increase of endogenous GLP-1 levels in terms of inflammatory stimuli like myocardial infarction and sepsis is protective, since blocking of the GLP-1-receptor worsened while genetic DPP4-deficiency or pharmacological DPP4 inhibition (leading to less degradation of endogenous GLP-1, thereby increased GLP-1 levels) improved myocardial function and survival.[10,24] GLP-1 might be in line with natriuretic peptides or IL-10, which are up-regulated following inflammatory stimuli and predict adverse clinical outcomes in patients with myocardial infarction but still remain organoprotective as endogenous counterregulatory factors.[25–29] Thus, although endogenous natriuretic peptide levels were associated with poor cardiovascular prognosis, blocking degradation of natriuretic peptides by pharmacological neprilysin inhibition improved cardiovascular prognosis in patients with heart failure.[30]

As previously shown, biomarkers including hs-Troponin T, NT-proBNP, and hsCRP as well as risk scores like the GRACE score are powerful tools for risk stratification in patients with myocardial infarction. Importantly, the combination of these established biomarkers with the GRACE score can enhance risk discrimination.[31] We found GLP-1 levels to have a similar predictive value as these established biomarkers in patients with acute myocardial infarction. Therefore, GLP-1 levels used alone or in combination with other biomarkers or risk scores might improve risk stratification and clinical decision making in patients with acute coronary syndrome. In addition, deciphering the role of GLP-1 as a potential novel biomarker of cardiovascular risk will foster our understanding of the gut—vascular axis as a yet fairly neglected field of system biology. While the

pathophysiological role of other biomarkers related to the immune system (hs-CRP and IL-6), myocardial infarction (Troponin T/I), myocardial stretch (NT-proBNP) or thrombosis (D-dimer) have been well described there is no robust data on gut hormones and cardiovascular risk.[32]

Limitations of the study

This study has several strengths and limitations. We do report strong association of GLP-1 levels with cardiovascular outcome and mortality which remained significant in complex statistical models and proved superior to established biomarkers at early time points following myocardial infarction. However, this observation does not imply causality, which cannot be assessed in the performed observational cross-sectional cohort study design with limited duration and number of events. Further, additional baseline characteristics including body mass index, waist circumference, fasting glucose, liver steatosis, alcohol intake, gout, and exercise—which were not collected in the current study—might have affected GLP-1 serum levels. Finally, we have no information on prediabetes and impaired glucose tolerance, which could have impact on the association of GLP-1 and cardiovascular prognosis.[33–35]

Future directions

Additional larger prospective studies with repeated GLP-1 measurements are warranted to further evaluate clinical applicability of GLP-1 as a novel biomarker in patients with acute myocardial infarction.

In conclusion, in patients hospitalized for myocardial infarction, GLP-1 levels are associated with cardiovascular events and proved to be superior to established biomarkers for early events. Moreover, admission GLP-1 levels added additional value to the GRACE risk score in NSTEMI patients. Future studies are needed to investigate whether GLP-1 can improve therapeutic decision making in NSTEMI/STEMI patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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