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RESEARCH LETTER

Association of Glucose-Dependent Insulinotropic Polypeptide Levels With Cardiovascular Mortality in Patients With Acute Myocardial Infarction

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The gut incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (GIP) are secreted by enteroendocrine cells following food intake leading to insulin secretion and glucose lowering.[1] This mode of action is currently used for the treatment of patients with type 2 diabetes mellitus.[2] Beyond its glucoregulatory function, glucagon-like peptide-1 receptor agonists exhibit direct cardio- and atheroprotective effects and have been shown to improve cardiovascular prognosis in high-risk patients with diabetes mellitus.[3] First experimental studies suggested the other gut incretin hormone GIP to also have beneficial cardiovascular effects.[4] Here, we investigated circulating GIP levels in high-risk patients with myocardial infarction. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set to 5%. The data that support the findings of this study are available from the corresponding author upon reasonable request.

We investigated the association of GIP serum levels at the time of hospital admission with cardiovascular prognosis in a cohort of 852 patients (67±13 years; 73% men) with acute myocardial infarction (34% ST-segment–elevation myocardial infarction, 66% non–ST-segment–elevation myocardial infarction). Our study was approved by an institutional review committee, and all subjects gave informed consent. GIP levels displayed no statistically significant correlation with cardiovascular risk factors (including smoking, hypertension, hypercholesterolemia, and diabetes mellitus), preexisting cardiovascular disease, and markers of heart failure and inflammation, as indicated by NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitivity C-reactive protein levels (Figure [A]). Modest inverse correlation of GIP levels with troponin T as a marker of acute cardiac injury was found (P=0.014) (Figure [A]).

We used Cox regression models to investigate the association between GIP and time-to-event outcomes specifying Efron's approximation to handle ties and checking the proportional hazards assumption using Schoenfeld residuals (R version 3.6). Kaplan-Meier curves (GIP median; cutoff, 69 pg/mL) and univariable Cox regression analyses showed that lower GIP levels were associated with an increased risk of cardiovascular mortality (hazard ratio of logarithmized GIP values: 0.520; 95% CI, 0.30–0.90; P=0.020; median follow-up, 311 days, 28 events, 17 patients with unknown cause of death were excluded from the analysis) (Figure [B and C]). GIP levels were not significantly associated with all-cause mortality (hazard ratio of logarithmized GIP values: 0.928; 95% CI, 0.68–1.26; P=0.63).

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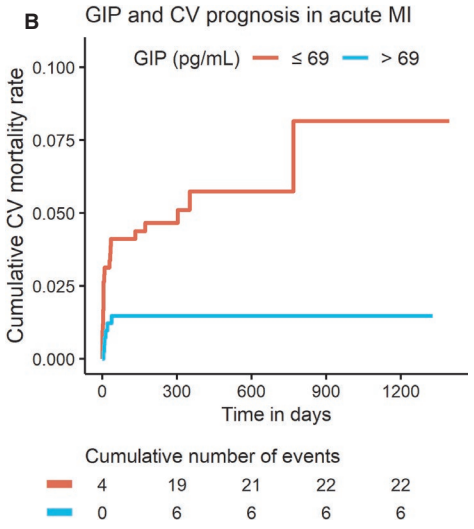
A Table Baseline characteristics

Characteristics		All patients (n=852)	GIP (pg/mL) ≤ 69 (n=425)	GIP (pg/mL) > 69 (n=427)	p-value
Demographics					
Age, years		66.8 ± 12.7	66.6 ± 12.9	67.0 ± 12.5	0.60
Sex (male)		625 (73.4%)	302 (71.1%)	323 (75.6%)	0.13
Cardiovascular risk factors					
Smoker		459 (58.9%)	228 (57.7%)	231 (60.0%)	0.52
Hypertension		616 (75.6%)	306 (75.4%)	310 (75.8%)	0.89
Hypercholesterolemia		422 (58.4%)	212 (58.24%)	210 (58.5%)	0.94
Diabetes mellitus		203 (25.0%)	91 (22.6%)	112 (27.3%)	0.12
Family history of CVD		284 (40.2%)	150 (40.9%)	134 (39.4%)	0.69
Risk markers at baseline					
hs-Troponin T (ng/L)		144 (46 - 494)	183 (48 - 592)	112 (40 - 377)	0.014
NT-proBNP (pg/mL)		663 (189 - 2196)	608 (165 - 2133)	703 (205 - 2272)	0.21
hs-CRP (mg/L)		4.2 (1.7 - 14.8)	4.3 (1.6 - 15)	4.1 (1.7 - 14.3)	0.99
Serum creatine kinase (U/L)		180 (107 - 398)	192 (109 - 477)	170.5 (106 - 344.5)	0.05
Serum creatinine (mg/dL)		0.9 (0.8 - 1.1)	0.9 (0.8 - 1.1)	1.0 (0.8 - 1.2)	0.019
Glucose (mg/dL)		129 (109 - 157)	127 (108 - 154)	130 (111 - 163)	0.16
Time since symptom onset	<3h	150 (20.9%)	74 (20.4%)	76 (21.5%)	0.93
	3-6h	129 (18%)	65 (17.9%)	64 (18.1%)	
	>6h	438 (61.1%)	224 (61.7%)	214 (60.5%)	



C Table Cox regression models for cardiovascular mortality in acute MI (HR: hazard ratio)

	Univariable model (n=835)		Model 1 (n=835)		Model 2 (n=595)		Model 3 (n=659)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
log(GIP)	0.52 (0.299, 0.902)	0.020	0.488 (0.276, 0.864)	0.014	0.473 (0.224, 0.999)	0.050	0.315 (0.142, 0.699)	0.005

Figure 1. Circulating GIP levels in patients with acute MI.
A, Baseline characteristics: continuous variables are expressed as mean±SD or median (Q1–Q3) in case of heavily skewed data. Categorical variables are shown as absolute and relative frequencies. **A**, Categories were established through the median GIP value. **B**, *P* value of the unpaired t test or the Wilcoxon rank-sum test in the case of (heavily skewed) continuous characteristics or *P* value of the χ^2 test in the case of nominal characteristics. **B** and **C**, Serum GIP levels are associated with cardiovascular prognosis in patients with acute MI. **B**, Kaplan-Meier cumulative event curves for cardiovascular mortality with patients separated by median GIP levels (cutoff, 69 pg/mL). **C**, Cox regression models for cardiovascular mortality in dependence of logarithmized GIP values. The crude model displays the univariable Cox regression model for log(GIP). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, and family history of cardiovascular disease. Model 3 was adjusted for all baseline variables with a $P<0.05$ in the univariable Cox regression analysis for cardiovascular mortality: age; diabetes mellitus; and logarithmized values of serum creatinine, NT-proBNP, hs-CRP, and glucose. Other candidate variables not selected were sex, smoking, hypertension, hypercholesterolemia, family history of cardiovascular disease, serum creatine kinase, time since symptom onset, and logarithmized values of hs-troponin T. CV indicates cardiovascular; CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-troponin T, high-sensitivity troponin T; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide;.

Bearing in mind the risk of overfitting, we considered 3 multivariable Cox models in which we adjusted for clinically or statistically relevant variables (model 1: age and sex; model 2: age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, and family history of cardiovascular disease; model 3: all baseline variables with a $P<0.05$ in the univariable Cox regression analysis for cardiovascular mortality, which were age, diabetes mellitus, and logarithmized values of serum creatinine, NT-proBNP, glucose, and high-sensitivity C-reactive protein). In all 3 multivariable models, the association between GIP levels and cardiovascular mortality remained significant, with similar hazard ratios as in the univariable Cox regression model (Figure [C]). In an additional model, we solely adjusted for high-sensitivity troponin, which did not affect the significant association of GIP levels and cardiovascular mortality (hazard ratio of logarithmized GIP values: 0.544; 95% CI, 0.30–1.00; $P<0.05$).

In summary, we found lower GIP levels to be associated with a poor cardiovascular outcome in high-risk patients with acute myocardial infarction. Our findings contrast to a recent population-based study reporting higher fasting GIP levels to be associated with adverse cardiovascular prognosis.[5] This might reflect differential regulation of GIP by nutritional stimuli or cardiac injury and needs further investigation. Importantly, experimental studies suggest GIP treatment to improve outcome in cardiovascular disease models, which does require translational investigations in humans. Future studies with larger cohorts and more events are needed to foster our understanding of the gut-heart axis as a yet fairly neglected field of system biology and

to elucidate whether the GIP system might open novel therapeutic approaches for the treatment of patients with cardiovascular disease.

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REFERENCES

1. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132:2131–2157. DOI: 10.1053/j.gastro.2007.03.054.
2. Lehrke M, Marx N. New antidiabetic therapies: innovative strategies for an old problem. *Curr Opin Lipidol*. 2012;23:569–575. DOI: 10.1097/MOL.0b013e328359b19f.
3. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Kober L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776–785. DOI: 10.1016/S2213-8587(19)30249-9.
4. Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a potential therapeutic target for atherosclerotic cardiovascular disease-a systematic review. *Int J Mol Sci*. 2020;21:1509. DOI: 10.3390/ijms21041509.
5. Jujić A, Atabaki-Pasdar N, Nilsson PM, Almgren P, Hakaste L, Tuomi T, Berglund LM, Franks PW, Holst JJ, Prasad RB, et al. Glucose-dependent insulinotropic peptide and risk of cardiovascular events and mortality: a prospective study. *Diabetologia*. 2020;63:1043–1054. DOI: 10.1007/s00125-020-05093-9.