Copeptin, IGFBP-1, and Cardiovascular Prognosis in Patients With Type 2 Diabetes and Acute Myocardial Infarction

A report from the DIGAMI 2 trial

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OBJECTIVE — To determine whether C-terminal provasopressin (copeptin) explains the prognostic importance of insulin growth factor binding protein-1 (IGFBP-1) in patients with myocardial infarction and type 2 diabetes.

RESEARCH DESIGN AND METHODS — Copeptin and IGFBP-1 were analyzed in 393 patients participating in the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 trial.

RESULTS — Copeptin was associated with IGFBP-1 (Spearman rank correlation test, $r = 0.53$; $P < 0.001$). During follow-up there were 138 cardiovascular events (cardiovascular death, myocardial infarction, and stroke). In univariate Cox proportional hazard regression analyses both biomarkers were predictors of events: the hazard ratio for log copeptin was 1.59 (95% CI 1.41–1.81; $P < 0.001$) and for log IGFBP-1 was 1.49 (1.26–1.77; $P < 0.001$). In the final model, adjusting for age and renal function, copeptin was the only independent predictor (1.35 [1.16–1.57]; $P < 0.001$).

CONCLUSIONS — Copeptin is an independent predictor of cardiovascular events and appears to at least partly explain the prognostic impact of IGFBP-1 in patients with type 2 diabetes and myocardial infarction. Copeptin may be a pathogenic factor to address to improve outcome in these patients.

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Copeptin, the C-terminal degradation part of the vasopressin prehormone, is a stable peptide suitable as a marker for the arginine vasopressin (AVP) system (1,2), which is activated by stress and plays an essential role in osmoregulation and the control of vascular tone (3). High levels of copeptin are linked to impaired cardiovascular prognosis (4). Another factor related to cardiovascular prognosis is insulin growth factor binding protein-1 (IGFBP-1), which modulates IGF-1 bioavailability (5,6). There may be a link between the AVP and IGF-1 systems since infusions of desmopressin, a vasopressin agonist, in patients with diabetes insipidus had a direct impact on IGFBP-1 levels (7).

This report, a substudy of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 trial, analyzes whether copeptin explains the prognostic importance of IGFBP-1 in patients with diabetes and myocardial infarction.

RESEARCH DESIGN AND METHODS

— Copeptin and IGFBP-1 were measured at hospital admission in 393 patients of the DIGAMI 2 cohort (8, online appendix Figure 1 available at http://care.diabetesjournals.org/cgi/content/full/dc10-0088/DC1). Copeptin was measured with a sandwich immunoassay (LUMI test C-terminal pro-AVP; BRAMHS, Henningsdorf/Berlin, Germany; lower detection limit 0.4 pmol/l, functional assay sensitivity [<20% interassay coefficient of variation] <1 pmol/l) (1,2). The IGFBP-1 concentrations in serum were determined by radioimmunoassay (sensitivity 3 μg/l and cardiovascular intra- and interassays 3 and 10%, respectively) according to Póvoa et al. (9).

Statistical methods

Differences between groups were assessed with Kruskal-Wallis, Jonckheere-Terpstra, or log-rank tests for trend. The association between continuous variables was studied with the Spearman rank correlation. Cox proportional hazard regression assessed the relation between copeptin, IGFBP-1, and cardiovascular events (a composite of cardiovascular death and nonfatal myocardial infarction or stroke). Known predictors of outcome in the DIGAMI 2 trial (age, creatinine clearance, glucose at admission, and previous heart failure) were adjusted for in univariable analyses. Age and creatinine clearance remained significant and were included in the final model. A two-tailed $P < 0.05$ was considered significant (SAS 9.2).

RESULTS

— For patient characteristics see online appendix Table 1. Copeptin varied between 0.97 and 1936.0 pmol/l (median 21.8; mean 62.4) and IGFBP-1 between 3.0 and 677.0 μg/l (median 23.0, mean 42.0).

During follow-up (median 2.5 years), cardiovascular events increased by increasing copeptin tertiles (log-rank test $P < 0.0001$; online appendix Fig. 3). Moreover, cardiovascular deaths within 90 days were related to higher copeptin levels at baseline (Jonckheere-Terpstra test $P < 0.0001$; online appendix).

There was a significant correlation be-

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Table 1—*Unadjusted and adjusted predictive ability of copeptin and IGFBP assessed by Cox proportional hazard regression*

	Cardiovascular event*			Cardiovascular death			Nonfatal reinfarction or stroke		
	n	HR (95% CI)	*P*	*n*	HR (95% CI)	*P*	*n*	HR (95% CI)	*P*
Univariable unadjusted ($n = 393$)									
log Copeptin	138	1.59 (1.41–1.81)	<0.001	77	1.81 (1.54–2.14)	<0.001	77	1.35 (1.13–1.61)	<0.001
log IGFBP-1	138	1.49 (1.26–1.77)	<0.001	77	1.99 (1.57–2.51)	<0.001	77	1.11 (0.88–1.39)	0.37
Multiple model including ($n = 393$) log copeptin and log IGFBP-1									
log Copeptin	138	1.53 (1.31–1.78)	<0.001	77	1.56 (1.27–1.92)	<0.001	77	1.43 (1.16–1.77)	<0.001
log IGFBP-1	138	1.10 (0.90–1.34)	0.35	77	1.41 (1.06–1.86)	0.017	77	0.87 (0.67–1.14)	0.32
Multiple model adjusted ($n = 380$)									
log Copeptin†	129	1.35 (1.16–1.57)	<0.001	70	1.43 (1.16–1.76)	<0.001	74	1.26 (1.03–1.54)	0.03

*CV death, myocardial infarction, or stroke. †Adjusted for age and creatinine clearance.

tween copeptin and IGFBP-1 (Spearman correlation coefficient 0.53; $P < 0.001$; online appendix Table 2). Both biomarkers correlated with age, BMI, creatinine clearance, and blood glucose but not with A1C. Sex did not influence copeptin levels, but higher levels were seen in patients above the median age, with renal function below or glucose levels above the median and in those with known heart failure. IGFBP-1 was higher in women and those above the median age or with renal function below or glucose levels above the median (online appendix Table 2).

Copeptin and IGFBP-1 were significant predictors of cardiovascular events in unadjusted analysis (Table 1). In the final model, adjusting for age and creatinine clearance, copeptin remained an independent predictor.

CONCLUSIONS — The present observation of a correlation between the levels of copeptin and IGFBP-1, combined with the stimulatory effect of desmopressin on IGFBP-1 (7), suggests a pathogenic relationship between vasopressin and IGFBP-1.

Activation of the AVP system, mainly regulated by serum osmolality (10), may be detrimental in patients with myocardial infarction by increasing left ventricular afterload due to vasoconstriction and preload due to renal water reabsorbtion (10). This study adds IGFBP-1 as a new effector of vasopressin-mediated stress response in myocardial infarction. The exact reasons are unclear, but there are plausible explanations.

IGFBP-1 modulates the bioavailable levels of IGF-1 and has both direct and IGF-1–mediated effects (11). IGFBP-1 is mainly produced by the liver (5) and largely regulated by inhibitory effects of insulin (12). The ratio between IGFBP-1 and insulin is increased in patients with myocardial infarction (6) and critical illness (13), perhaps as a consequence of hepatic insulin resistance induced by hypoxia and proinflammatory cytokines (11–13).

The newly described relationship between copeptin and insulin resistance (14) adds to this relation with a potentially negative impact on cardiovascular outcome. Another possibility is that IGFBP-1 activation may be a result of vasopressin receptor activation. This might have therapeutic implications because clinical trials with antagonists of these receptors (vaptans) have produced mixed results, however, so far without cardiovascular benefits. It may be that the present vaptans act on the wrong set of receptors in the present clinical scenario. Copeptin was higher in patients with previously known heart failure. Indeed heart failure, a predictor of events in the DIGAMI 2 trial, disappeared after adjusting for copeptin, indicating a pathogenic relationship.

The copeptin levels in this present population are higher than those described in healthy individuals (2) but not higher than in other patients with myocardial infarction, although copeptin seems elevated in patients with diabetes (4). This may reflect the high proportion of glucometabolic perturbations in patients with myocardial infarction (15).

This study has limitations. Although it was a prospectively planned biochemical part of the DIGAMI 2 trial, this study is of observational character and thereby limited to the available subpopulation. The lack of a measure of hemodynamic confounders such as serum osmolality may be seen as draw back. However, copeptin and IGFBP-1 were intentionally sampled soon after hospital admission, i.e., before the initiation of study-related or other treatments that could have influenced the biomarkers.

In conclusion, copeptin is an independent predictor of cardiovascular events and appears, at least partly, to explain the prognostic impact of IGFBP-1 in patients with type 2 diabetes and myocardial infarction. The present results are hypothesis generating, encouraging further studies on the pathophysiological relation between copeptin and IGFBP-1 and whether copeptin per se is a factor to be addressed in order to improve the outcome in these patients.

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N.G.M. is employed by BRAHMS AG, which is involved in the development of in vitro diagnostics and has developed an assay for the measurement of copeptin. No other potential conflicts of interest relevant to this article were reported.

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