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.

Diabetes Care 33:1604–1606, 2010

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 increasing copeptin tertiles (log-rank test for trend; P < 0.0001; online appendix Fig. 3). 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-
between 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 reabsorption (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 because of 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 a drawback. 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.
Copeptin and IGFBP-1

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