C-terminal-ProVasopressin (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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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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**Objective:** To study if copeptin explains the prognostic importance of 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 DIGAMI 2 trial.

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

**Conclusions:** Copeptin is an independent predictor of cardiovascular events and appears at least partly explains 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.
Copeptin, the c-terminal degradation part of the vasopressin pre-hormone, is a stable peptide suitable as a marker for the arginine vasopressin (AVP system) which is activated by stress and plays an essential role in osmoregulation and the control of vascular tone. High levels of copeptin are linked to impaired cardiovascular prognosis. Another factor related to cardiovascular prognosis is Insulin growth factor binding protein-1 (IGFBP-1), involved in IGF-1 bioavailability. 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. This report, a substudy to DIGAMI 2, analyzes if copeptin explains the prognostic importance of IGFBP-1 in patients with diabetes and myocardial infarction.

METHODS
Copeptin and IGFBP-1 was measured at hospital admission in 393 patients of the DIGAMI 2 cohort and the Online Appendix available at http://care.diabetesjournals.org. Copeptin was measured with a sandwich immunoassay (LUMI test C-terminal pro-AVP: BRAMHS AG, 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 RIA (sensitivity 3 µg/l and cardiovascular intra- and interassays 3 and 10%) according to Povoa et al. (9).

Statistical methods. Differences between groups were assessed with Kruskal-Wallis, Jonckheere-Terpstra or Log-rank test for trend. The association between continuous variables was studied with the Spearman’s Rank Correlation. Cox’s proportional hazard regression assessed the relation between copeptin, IGFBP-1 and cardiovascular events (a composite of cardiovascular death and non-fatal myocardial infarction or stroke). Known predictors of outcome in DIGAMI 2 (age, creatinine clearance and 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 level. (SAS 9.2).

RESULTS
For patient characteristics see Appendix. Copeptin varied between 0.97 and 1936 (median 21.8; mean 62.4) pmol/l and IGFBP-1 between 3.0 and 677.0 (median 23, mean 42.0) µg/l.

During follow up (median 2.5 years) cardiovascular events increased by increasing copeptin tertiles (log-rank test p < 0.001; Appendix). Moreover cardiovascular deaths within 90 days were related to higher copeptin levels at baseline (Jonckheere-Terpstra test; p<0.0001; Appendix). There was a significant correlation between copeptin and IGFBP-1 (Spearman correlation coefficient 0.53; p <0.001; Appendix). Both biomarkers correlated with age, BMI, creatinine clearance and blood glucose but not with HbA1c. Gender did not influence copeptin levels while higher levels were seen in patients above median age, with renal function below or glucose above median and in those with known heart failure. IGFBP-1 was higher in women and those above median age or renal function below or glucose above median; Appendix).

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 as 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 a consequence of hepatic insulin resistance induced by hypoxia and pro-inflammatory 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 since 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 DIGAMI 2, 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).

Study limitations. Although this study was a prospectively planned biochemical part of DIGAMI 2 it is still of observational character, 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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Conflict of interest. NGM is employed by B.R.A.H.M.S. AG, which is involved in the development of in vitro diagnostics, and has developed an assay for the measurement of
copeptin. LM, LR, KB, JÖ and SC have no conflicts of interest to report.

REFERENCES
Table 1. Unadjusted and adjusted predictive ability of copeptin and IGFBP assessed by Cox’s proportional hazard regression. (HR = Hazard Ratio; CI = Confidence Interval)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardiovascular event (CV death, MI or stroke)</th>
<th></th>
<th>Cardiovascular death</th>
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<th>Non-fatal re-infarction or stroke</th>
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<tr>
<td></td>
<td>n</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>n</td>
<td>HR (95% CI)</td>
<td>p-value</td>
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<tr>
<td><strong>Univariable unadjusted</strong> (n = 393)</td>
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<tr>
<td>log Copeptin</td>
<td>138</td>
<td>1.59 (1.41-1.81)</td>
<td>p&lt;0.001</td>
<td>77</td>
<td>1.81 (1.54-2.14)</td>
<td>p&lt;0.001</td>
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<tr>
<td>log IGFBP-1</td>
<td>138</td>
<td>1.49 (1.26-1.77)</td>
<td>p&lt;0.001</td>
<td>77</td>
<td>1.99 (1.57-2.51)</td>
<td>p&lt;0.001</td>
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<td><strong>Multiple model including log Copeptin and log IGFBP-1</strong> (n = 393)</td>
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<tr>
<td>log Copeptin</td>
<td>138</td>
<td>1.53 (1.31-1.78)</td>
<td>p&lt;0.001</td>
<td>77</td>
<td>1.56 (1.27-1.92)</td>
<td>p&lt;0.001</td>
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<td>log IGFBP-1</td>
<td>138</td>
<td>1.10 (0.90-1.34)</td>
<td>p=0.35</td>
<td>77</td>
<td>1.41 (1.06-1.86)</td>
<td>p=0.017</td>
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<td><strong>Multiple adjusted</strong> (n = 380)</td>
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<tr>
<td>log Copeptin*</td>
<td>129</td>
<td>1.35 (1.16-1.57)</td>
<td>p&lt;0.001</td>
<td>70</td>
<td>1.43 (1.16-1.76)</td>
<td>p&lt;0.001</td>
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* adjusted for age, creatinine clearance