Copeptin, a Surrogate Marker for Arginine Vasopressin, Is Associated With Cardiovascular and All-Cause Mortality in Patients With Type 2 Diabetes (ZODIAC-31)

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OBJECTIVE—Copeptin, a surrogate marker for arginine vasopressin, has been associated with cardiovascular (CV) events and mortality in patients with type 2 diabetes complicated by end-stage renal disease or acute myocardial infarction. For stable outpatients, these associations are unknown. Our aim was to investigate whether copeptin is associated with CV and all-cause mortality in patients with type 2 diabetes treated in primary care.

RESEARCH DESIGN AND METHODS—Patients with type 2 diabetes participating in the observational Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) study were included. Cox regression analyses with age as time scale were used to assess the relationship of baseline copeptin with CV and all-cause mortality.

RESULTS—We included 1,195 patients (age 67 ± 12 years, 44% male). Median baseline copeptin concentration was 5.4 (interquartile range [IQR] 3.1–9.6) pmol/L. After a median follow-up of 5.9 (IQR 3.2–10.1) years, 345 patients died (29%), with 148 CV deaths (12%). Log_2 copeptin was associated with CV (hazard ratio 1.17 [95% CI 0.99–1.39]; $P = 0.068$) and all-cause mortality (1.22 [1.09–1.36]; $P = 0.001$) after adjustment for age, sex, BMI, smoking, systolic blood pressure, total cholesterol to HDL ratio, duration of diabetes, HbA_{1c}, treatment with ACE inhibitors and angiotensin receptor blockers, history of CV diseases, log serum creatinine, and log albumin to creatinine ratio; however, copeptin did not substantially improve risk prediction for CV (integrated discrimination improvement 0.14% [IQR −0.27 to 0.55%]) and all-cause mortality (0.77% [0.17–1.37%]) beyond currently used clinical markers.

CONCLUSIONS—We found copeptin to be associated with CV and all-cause mortality in patients with type 2 diabetes treated in primary care. Intervention studies should show whether the high CV risk in type 2 diabetes can be reduced by suppression of vasopressin, for example by reducing salt intake.

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The prevalence of type 2 diabetes and its complications are increasing worldwide (1). One of the major complications in type 2 diabetes is cardiovascular disease (CVD), and CVD is the main cause of morbidity and mortality in this patient group (2).

Arginine vasopressin (AVP), or antidiuretic hormone, is a hormone that exerts cardiovascular (CV) and renal effects (3). Several studies have reported that AVP levels are elevated in animals and patients with diabetes (4–7). Increased levels of AVP may have long-term deleterious effects. AVP acts through three different vasopressin receptors, the V_{1a}, V_2, and V_3 (or V_{1b}) receptors, which mediate vasoconstriction, stimulate water retention, and facilitate secretion of ACTH, respectively (3). High concentrations of plasma AVP are known to stimulate V_{1a} receptors preferentially (8), which may contribute to the CV complications in type 2 diabetes.

Despite the pivotal role of AVP in CVD, technical difficulties related to AVP's small size, short plasma half-life, and association with platelets in the circulation have hindered the large-scale clinical use of AVP as a biomarker (3,9,10). Vasopressin is synthesized from a polypeptide precursor that contains AVP, neurophysin II, and copeptin (3). Copeptin, or COOH-terminal proarginine vasopressin, is released in equimolar amounts to AVP during precursor processing and has been found to be a stable and sensitive surrogate marker for AVP (11,12).

A recent study of Fenske et al. (8) showed copeptin levels to be strongly associated with CV events and mortality in patients with type 2 diabetes and end-stage renal disease. Copeptin was also found to be associated with CV events in patients with acute myocardial infarction and type 2 diabetes (13). To our knowledge, however, these associations have not been demonstrated for stable, ambulatory patients with type 2 diabetes. This

is of particular interest, because it could point to a new modifiable system for treatment and prevention of CV events and mortality in type 2 diabetes (8,14). Our primary objective was to assess the association of baseline plasma copeptin level with CV and all-cause mortality in a population of patients with type 2 diabetes treated in primary care. Our secondary aim was to investigate the additional predictive value of copeptin for risk prediction of CV and all-cause mortality in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study group
The Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) study was initiated in 1998 in the Zwolle region of the Netherlands. The design and details of this study have been published elsewhere (15,16). In this study, general practitioners were assisted by hospital-based diabetes specialist nurses in their care of patients with type 2 diabetes. In the first year, 1,143 patients with type 2 diabetes were included in this prospective cohort study. In 2001, additional 546 patients with type 2 diabetes enrolled, for a combined cohort of 1,689 patients (17). Baseline plasma copeptin values were measured in 1,257 patients (74%). In this study, we included 1,195 patients (95%) with complete data. The ZODIAC study was approved by the local medical ethics committee, and all patients provided informed consent.

Data collection and measurements
Baseline data, which were collected in 1998 and 2001, consisted of a full medical history, including a history of CVD, use of medication, and tobacco consumption. Patients were considered to have a history of CVD if they had a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, or transient ischemic attack. Laboratory and physical assessment data were collected annually and included nonfasting lipid profile, HbA_{1c}, serum creatinine (SCr), urinary albumin to creatinine ratio (ACR), and blood pressure. SCr was measured by a kinetic colorimetric Jaffe method (Modular P Analyzer; Roche Almere, the Netherlands), ACR was measured by immunonephelometry (Behring Nephelometer; Behring Diagnostics, Mannheim, Germany), and blood pressure was measured twice with a Welch Allyn sphygmomanometer in the supine position after at least 5 min of rest. The creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation was used to obtain the estimated glomerular filtration rate (eGFR) (18).

Copeptin was measured in plasma samples collected at baseline and kept frozen at −80°C until analysis in 2010. Morgenthaler et al. (12) showed that prolonged frozen storage and repeated freeze-thaw cycles have no effect on copeptin values. Plasma copeptin was measured with a sandwich immunoassay (B.R.A.H.M.S. GmbH, Hennigsdorf, Germany), which was based on the assay described by Morgenthaler et al. (12). Measurement of copeptin was performed in batches. The lower detection limit was 0.4 pmol/L, the interassay coefficient of variation was <6% for copeptin concentrations >6 pmol/L, and the functional assay sensitivity (20% interassay coefficient of variation) was <1 pmol/L.

Clinical end points
In this study, we examined the association between baseline copeptin concentration and two coprimary clinical end points: CV mortality and all-cause mortality. In 2009, vital status and cause of death were retrieved from records maintained by the hospital and the general practitioners for the first 1,143 patients. For the additional 546 patients, vital status and cause of death were retrieved in 2005. Cause of death was coded according to the ICD-9. CV death was defined as any death in which the principal cause of death was CV in nature (ICD-9 codes 390–459).

Statistical analyses
Statistical analyses were performed with SPSS version 18.0 for Windows (IBM Corp., Armonk, NY) and STATA version 11 (StataCorp LP, College Station, TX). Results are expressed as mean ± SD or median (interquartile range [IQR]) for normally distributed and nonnormally distributed data, respectively. Nominal data are presented as the total number of patients with percentage (*n* [%]). A two-sided $P < 0.05$ was considered to indicate statistical significance.

For illustrative purposes, the study population was subdivided into tertiles according to baseline copeptin concentration, and data are presented accordingly to visualize associations with copeptin. Because copeptin concentrations are significantly higher in men than in women (19), tertiles were sex-stratified. *P* values for differences in copeptin tertiles were assessed with ANOVA for normally distributed continuous data, the Kruskal-Wallis test for nonnormally distributed data, and the χ^2 test for nominal data. Multivariable linear regression analyses were used to investigate whether baseline copeptin concentration was associated with the clinical parameters. Because copeptin values were nonnormally distributed, logarithmic transformation (base 2) was applied to fulfill the criteria for linear regression analyses.

We investigated whether there were differences in baseline characteristics of patients with and without copeptin measurement. *P* values for differences between patients with and without copeptin measurement were assessed with the independent sample *t* test for normally distributed continuous data, the Mann-Whitney *U* test for nonnormally distributed data, and the χ^2 test for nominal data.

Cox regression analyses were used to test whether there were interactions between copeptin and clinical parameters including age, sex, history of CVD, and duration of diabetes. We used Cox regression analyses with age as time scale in which we accounted for left truncation (delayed entry) to analyze the risk of CV and all-cause mortality during follow-up. We applied $\log_2$ transformation of copeptin values so the hazard ratios (HRs) derived from Cox regression analyses were expressed as an increase in risk per doubling of baseline copeptin values. Various models were built to adjust for possible confounders. First, the univariable association of $\log_2$ copeptin with CV and all-cause mortality was investigated. Second, the model was adjusted for age and sex. Finally, the model was additionally adjusted for CV risk factors and medication that could potentially influence copeptin secretion (BMI, smoking, systolic blood pressure, total cholesterol to HDL ratio, duration of diabetes, HbA_{1c}, history of CVD, use of ACE inhibitors or angiotensin receptor blockers, log SCr, and log ACR). The assumption of proportional hazards for baseline predictors was investigated by inspecting the Schoenfeld residuals. As sensitivity analyses, we repeated the Cox regression analyses with follow-up time as time scale. Furthermore, we investigated the effect of inclusion of time-dependent covariates (age, systolic blood pressure, total cholesterol to HDL ratio, duration of diabetes, HbA_{1c}, SCr, and

ACR) in Cox regression analyses. In addition, Cox regression analyses were used to test whether an association existed between the presence or absence of a copeptin measurement and CV and all-cause mortality in the combined cohort of 1,689 patients.

Discrimination, a measure to evaluate how well a model distinguishes between patients who died and those who survived while taking follow-up time into account, was assessed with the Harrell's C statistic (20). The additional value of copeptin for the risk prediction of CV and all-cause mortality was assessed in terms of integrated discrimination improvement (IDI) and net reclassification improvement (NRI) (21). The IDI can be interpreted as the difference between model-based probabilities for events and nonevents for the models with and without copeptin. The NRI is calculated by assessing the net improvement in risk

classification (<10, 10–20, 20–30, and >30%) for events and nonevents separately. Calibration, a measure to evaluate how well predicted probabilities agree with observed risks, was assessed with the Grønessby and Borgan goodness-of-fit likelihood ratio test (22).

RESULTS

Patient characteristics
A total of 1,195 patients with type 2 diabetes were included in this study. Mean age of the study population was 67 ± 12 years, and 524 patients (44%) were male. Median copeptin concentration was 5.4 (IQR 3.1–9.6) pmol/L. Median copeptin concentration was significantly higher in men than in women (7.4 [4.5–11.5] vs. 4.1 [2.6–7.3] pmol/L, respectively; $P < 0.0001$). Baseline patient characteristics are presented as sex-stratified tertiles in Table 1. Variables that

were significantly different between tertiles of copeptin concentrations were age, history of CVD, BMI, total cholesterol to HDL ratio, duration of diabetes, HbA_{1c}, ACR, SCr, and eGFR (Table 1). Multivariable linear regression analyses showed that sex (b = -0.57; $P < 0.001$), age (b = 0.01; $P < 0.001$), BMI (b = 0.03; $P < 0.001$), HbA_{1c} (b = 0.11; $P < 0.001$), systolic blood pressure (b = -0.004; $P < 0.001$), log ACR (b = 0.21; $P < 0.001$), and log SCr (b = 3.69; $P < 0.001$) were associated with baseline copeptin concentrations.

In addition, we investigated whether there were differences in baseline characteristics of patients with and without copeptin measurement (Supplementary Table 1). Only baseline serum creatinine values were slightly higher in patients without copeptin measurements (98 $\pm$ 23 μmol/L) than in patients with copeptin measurements (95 $\pm$ 22 μmol/L, P = 0.04). We found no other significant differences

Table 1—*Baseline patient characteristics of the study population presented as sex-stratified tertiles of copeptin concentration*

	Tertile 1	Tertile 2	Tertile 3	P value
Copeptin tertile cutoffs (pmol/L)				
Male	<5.2	5.2–9.9	>9.9	—
Female	<3.1	3.1–5.9	>5.9	—
n				
Male	175	174	175	—
Female	224	227	219	—
Demographics				
Age (years)	65 ± 10	66 ± 12	69 ± 12	<0.001
Smoking	79 (19.8)	73 (18.2)	61 (15.5)	0.3
History of CVD	114 (28.5)	129 (32.2)	167 (42.4)	<0.001
Body composition				
BMI (kg/m^2)	28.5 ± 4.2	29.3 ± 4.8	29.9 ± 5.2	<0.001
Blood pressure				
Systolic blood pressure (mmHg)	153 ± 24	153 ± 25	151 ± 24	0.3
Diastolic blood pressure (mmHg)	84 ± 10	83 ± 10	84 ± 10	0.8
Use of ACE inhibitors or ARBs	102 (25.5)	102 (25.4)	117 (29.7)	0.3
Lipids				
Total cholesterol (mmol/L)	5.4 ± 1.0	5.6 ± 1.1	5.6 ± 1.1	0.1
HDL cholesterol (mmol/L)	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.6	0.5
Triglycerides (mmol/L)	2.0 (1.5–2.8)	2.1 (1.5–3.1)	2.1 (1.5–3.2)	0.2
Total cholesterol to HDL ratio	4.7 ± 1.5	5.0 ± 1.5	5.0 ± 1.4	0.04
Use of lipid-lowering drugs (*n*, %)	61 (15.3)	62 (15.5)	50 (12.7)	0.5
Glucose homeostasis				
Duration diabetes (years)	4.0 (1.8–9.0)	4.0 (1.8–8.9)	5.0 (2.0–10.0)	0.002
HbA_{1c} (%)	6.8 (6.2–7.8)	7.0 (6.3–8.2)	7.3 (6.5–8.4)	<0.001
HbA_{1c} (mmol/mol)	51 (44–62)	53 (45–66)	56 (48–68)	<0.001
Renal function				
ACR (mg/mmol)	1.6 (0.9–4.0)	1.7 (0.8–6.1)	2.7 (1.0–8.2)	<0.001
SCr (μmol/L)	90 ± 14	91 ± 16	103 ± 29	<0.001
eGFR (mL/min/1.73 m^2)	68 ± 14	67 ± 15	59 ± 18	<0.001

Data are mean ± SD, *n* (%), and median (IQR). ACE, angiotensin-converting enzyme; ACR, urinary albumin to creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate per Chronic Kidney Disease Epidemiology Collaboration equation (18); HDL, high-density lipoprotein.

between baseline characteristics of patients with and without copeptin measurements.

Copeptin as a predictor of mortality
After a follow-up period of 10 years for the patients entering the study in 1998 and 3 years for those included in 2001, 345 of 1,195 included patients had died (29%), with 148 deaths (12%) attributable to CV causes. All-cause deaths (152 males [29%] vs. 193 females [29%]; *P* = 0.9) and CV deaths (64 males [12%] vs. 84 females [13%]; *P* = 0.9) were not more common among male subjects than among female subjects. Furthermore, there was no difference in median follow-up time for male and female subjects (5.5 [IQR 3.1–10.1] vs. 6.2 [3.2–10.1] years, respectively; *P* = 0.4). The median baseline copeptin concentration for survivors (4.9 [IQR 3.0–8.5] pmol/L) was significantly lower than both the median copeptin level of patients who had died of CV causes (7.9 [3.9–13.8] pmol/L) and the median copeptin level of patients who had died of all causes during follow-up (7.3 [3.7–13.0] pmol/L; *P* < 0.0001).

Cox regression analyses were used to investigate whether there were interactions between copeptin and clinical parameters including age, sex, history of CVD, and duration of diabetes. We found no significant interactions between copeptin and these clinical parameters.

In univariable Cox regression analyses with age as time scale, $\log_2$ copeptin was significantly associated with CV mortality (HR 1.55 [95% CI 1.34–1.80]; *P* < 0.001) and all-cause mortality (1.39 [1.26–1.53]; *P* < 0.001). The association of copeptin with all-cause mortality remained significant after adjustment for the various confounders (Table 2). The Schoenfeld residuals showed no substantial deviations, supporting the assumption of proportional hazards.

As sensitivity analyses, we repeated the Cox regression analyses with follow-up time as time scale (Table 3). The HRs and 95% CIs of the adjusted models in the sensitivity analyses were not materially different from the analyses with age as time scale. In the Cox regression models with follow-up time as time scale, the associations of copeptin with CV and all-cause mortality remained significant after adjustment for the different confounders (Table 3).

We also investigated the influence of time-dependent covariates in Cox regression analyses (Supplementary Table 2). In the fully adjusted models, $\log_2$ copeptin was significantly associated with CV mortality (HR 1.21 [95% CI 1.03–1.42]; *P* = 0.02) and all-cause mortality (1.23 [1.10–1.36]; *P* < 0.001).

Furthermore, we tested whether an association existed between the presence or absence of a copeptin measurement and CV and all-cause mortality in the combined cohort of 1,689 patients. In univariable and multivariable Cox regression analyses we found no association of the presence or absence of a copeptin measurement with CV and all-cause mortality.

Predictive value of copeptin
The additional value of copeptin for risk prediction of CV and all-cause mortality was assessed in terms of discrimination (Harrell's C statistic), NRI, and IDI (Table 4). Harrell's C statistics for models 2 and 3 without copeptin predicting CV mortality were 0.75 (0.71–0.78) and 0.80 (0.77–0.84), respectively. Harrell's C statistics for models 2 and 3 without copeptin predicting all-cause mortality were 0.77 (0.75–0.80) and 0.79 (0.77–0.82), respectively. Harrell's C statistics in Table 4 show that the more confounders we adjusted for, the better the model predicted CV and all-cause mortality. The Grønessby and Borgan *P* values in Table 4 indicate that predicted probabilities correspond well with observed risks (except for model 1 predicting all-cause

mortality), so the models were well calibrated. The IDI and NRI values for model 2 predicting CV mortality were 2.68% and 16.93%, respectively, indicating that copeptin had additional value on top of age and sex for risk prediction of CV mortality. In the fully adjusted models, however, the IDI and NRI values appeared to be <2%, indicating that copeptin did not substantially improve risk prediction for CV and all-cause mortality beyond currently used clinical markers.

CONCLUSIONS—In this prospective cohort of 1,195 patients with type 2 diabetes treated in primary care, we found copeptin to be associated with CV and all-cause mortality. After adjustment for established CV risk factors, we observed only a trend between copeptin and CV mortality, whereas the association of baseline plasma copeptin with all-cause mortality remained significant. Our findings are of particular interest because the AVP system is potentially modifiable through pharmacological and nonpharmacological interventions and could provide a possible target for treatment and prevention of CV events and mortality in type 2 diabetes.

Several studies have reported that plasma AVP levels are elevated in animals and patients with diabetes (4–7). AVP promotes water reabsorption through stimulation of V_2 receptors, and it is suggested that increased levels of AVP limit glucose-induced water loss in patients with diabetes (23).

Increased levels of AVP may, however, have long-term deleterious renal and CV effects. In experimental animal studies, as well as in humans, it has been shown that AVP contributes to hyperfiltration, albuminuria, and renal hypertrophy in diabetes (24,25). This notion is supported by the renal protective effects of AVP inhibition by drinking water or chronic treatment with a V_2 receptor antagonist in rats with renal failure (26,27) and diabetes (28).

High concentrations of plasma AVP are known to stimulate V_{1a} receptors preferentially (8), which results in coronary vasoconstriction (29), increasing afterload, ventricular stress, and cardiac hypertrophy (8,30,31). Several studies have reported that copeptin, a surrogate for AVP, is associated with CV events and mortality in patients with CVD (acute myocardial infarction, heart failure, and stroke) (3). A recent study of Fenske et al. (19)

Table 2—*Association of baseline $\log_2$ copeptin concentrations with CV and all-cause mortality in Cox regression analyses with age as time scale*

Model	CV mortality		All-cause mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
1	1.55 (1.34–1.80)	<0.001	1.39 (1.26–1.53)	<0.001
2	1.51 (1.30–1.77)	<0.001	1.36 (1.22–1.51)	<0.001
3	1.17 (0.99–1.39)	0.068	1.22 (1.09–1.36)	0.001

Model 1 is the crude model; model 2 is adjusted for age and sex; model 3 is adjusted for age, sex, BMI, smoking, systolic blood pressure, cholesterol to HDL ratio, duration of diabetes, HbA$_{1c}$, history of CVD, use of ACE inhibitors or angiotensin receptor blockers, log SCr, and log ACR.

Table 3—Association of baseline log$_2$ copeptin concentrations with CV and all-cause mortality in Cox regression analyses with follow-up time as time scale

	CV mortality		All-cause mortality	
Model	HR (95% CI)	P value	HR (95% CI)	P value
1	1.74 (1.49–2.04)	<0.001	1.57 (1.42–1.74)	<0.001
2	1.54 (1.32–1.80)	<0.001	1.37 (1.24–1.52)	<0.001
3	1.19 (1.00–1.41)	0.04	1.23 (1.10–1.37)	<0.001

Model 1 is the crude model; model 2 is adjusted for age and sex; model 3 is adjusted for age, sex, BMI, smoking, systolic blood pressure, cholesterol to HDL ratio, duration of diabetes, HbA$_{1c}$, history of CVD, use of ACE inhibitors or angiotensin receptor blockers, log SCr, and log ACR.

showed that copeptin is associated with CV events, sudden death, and all-cause mortality in patients with type 2 diabetes and end-stage renal disease.

Stimulation of V$_3$ (V$_{1b}$) receptors through AVP results in the release of ACTH, which stimulates cortisol release from the adrenal gland (3). AVP-induced ACTH release is reported to be less sensitive to feedback inhibition by glucocorticoids than ACTH induced by corticotropin-releasing hormone (32), which might worsen multiple aspects of the metabolic syndrome.

Median copeptin concentration of this study group was 5.4 (range 0.9–85.7) pmol/L, which is higher than the median value of 4.2 (range 1–13.8 pmol/L) pmol/L measured in healthy subjects (33). In line with previous studies, we found baseline plasma copeptin to be associated with renal function and albuminuria (34,35).

In addition, we found that baseline copeptin concentration was associated with CV and all-cause mortality; however, we found no differences in the number of deaths, number of CV deaths, or follow-up time between male and female subjects. This lack of difference is consistent with the literature on CV risk in diabetes, which indicates that women with diabetes have a higher relative risk for CV events than men with diabetes (36,37). Furthermore, copeptin values have consistently been shown to be higher in males than in females, even in healthy subjects (12,19). Risk categories that are based on copeptin level or reference values for copeptin concentrations should therefore be sex specific.

Several studies have shown that copeptin measurement has diagnostic and prognostic value in patients with acute CVD (3). Because copeptin was found to be associated with CV and all-cause mortality in patients with type 2 diabetes, we investigated whether copeptin had additional value for risk prediction of CV and all-cause mortality. In this study population, copeptin did not substantially improve risk prediction for CV and all-cause mortality beyond currently used clinical markers; however, copeptin was found to be associated with several CV risk factors (BMI, HbA$_{1c}$, systolic blood pressure, SCr, and ACR), and copeptin substantially improved risk prediction for CV mortality beyond age and sex. Thus copeptin might be a unified marker

for these known causes of CVD and therefore useful to discriminate patients who could benefit from intensification of therapy (38).

We acknowledge that this study has several limitations. First, given the observational nature of this study, it is impossible to draw a definite conclusion about the causality of the association of copeptin with CV and all-cause mortality. Second, selection bias may have occurred because patients whose copeptin had not been measured were excluded from statistical analysis. In additional Cox regression analyses, however, we found no significant association of the presence or absence of a copeptin measurement with CV and all-cause mortality. Third, blood samples were taken without restriction on food or water intake, which could have influenced plasma osmolarity and consequently copeptin concentration. Furthermore, measured plasma osmolarity, data required to calculate plasma osmolarity, and data on the use of diuretics were not available in this study group, which is a limitation of the current study because plasma osmolality and plasma volume are determinants of AVP secretion. In addition, no data on plasma albumin levels and total plasma protein were available in the current study. It could have been interesting to include these measures, because plasma albumin and protein may influence plasma osmolality and subsequently levels of AVP. Finally, the number of CV deaths in this study population was relatively small, which limits the number of covariates used in Cox regression analyses. It has been suggested that for each variable included in the model at least 10 events are required (20). With inclusion of 13 variables in the final Cox regression models, we are approaching the maximum number of variables allowed by the number of 148 CV deaths.

A strength of this study is that it is the first to investigate the association of copeptin with CV and all-cause mortality in patients with type 2 diabetes. In addition, this study included a relatively large observational cohort of patients with type 2 diabetes with a relatively long follow-up period (10 years) and a reasonable number of events (all-cause mortality). We therefore could prospectively investigate the association of baseline plasma copeptin levels with CV and all-cause mortality.

In conclusion, in this cohort of patients with type 2 diabetes, plasma

Table 4—Additional value of baseline log$_2$ copeptin concentrations in risk prediction compared with established CV risk markers

Model	Harrell's C (95% CI)	IDI (%) (95% CI)	NRI (%) (95% CI)	Grønnessby and Borgan
CV mortality				
1	0.63 (0.59–0.68)	NA	NA	0.10
2	0.76 (0.72–0.80)	2.68 (1.43–3.93)	16.93 (6.53–27.33)	0.98
3	0.81 (0.77–0.84)	0.14 (−0.27 to 0.55)	1.82 (−4.11 to 7.76)	0.15
All-cause mortality				
1	0.63 (0.59–0.66)	NA	NA	0.01
2	0.78 (0.75–0.80)	2.47 (1.45–3.50)	2.14 (−2.99 to 7.27)	0.84
3	0.80 (0.77–0.82)	0.77 (0.17–1.37)	0.55 (−3.36 to 4.46)	0.53

Model 1 is the crude model; model 2 is adjusted for age and sex; model 3 is adjusted for age, sex, BMI, smoking, systolic blood pressure, cholesterol to HDL ratio, duration of diabetes, HbA$_{1c}$, history of CVD, use of ACE inhibitors or angiotensin receptor blockers, log SCr, and log ACR. NA, not applicable.

copeptin, a surrogate marker for AVP, was associated with CV and all-cause mortality. These findings suggest that AVP may play a role in CV complications of type 2 diabetes and that interventions intended to lower AVP (e.g., by limiting sodium intake, improving glycemic control, and improving or preventing nephropathy-associated albuminuria) may be beneficial for the prevention of CV complications in type 2 diabetes. Water supplementation in patients without low serum albumin, edema, or risk for hyponatremia would also be a possible means of lowering AVP secretion. Furthermore, copeptin might be a unified marker for known causes of CVD and might be useful to discriminate patients who would benefit from intensification of therapy.

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