NT-proBNP and Echocardiographic Parameters for Prediction of Cardiovascular Outcomes in Patients with CKD Stages G2–G4

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Abstract

Background and objectives Natriuretic peptides and echocardiographic parameters both predict cardiovascular events in patients with CKD. However, it is unknown whether simultaneous assessment of amino–terminal probrain natriuretic peptide (NT-proBNP) and echocardiographic parameters provides complementary or redundant predictive information; in the latter case, one of these two might be dispensable. We aimed to analyze the implications of using NT-proBNP alone, echocardiographic parameters alone, or a combination of both for prediction of adverse cardiovascular outcome.

Design, setting, participants, & measurements Within the longitudinal Cardiovascular and Renal Outcome in CKD 2–4 Patients—The Fourth Homburg Evaluation Study, we prospectively studied 496 patients with CKD stages G2–G4, in whom we measured NT-proBNP. Left ventricular mass index, left atrial volume index, diastolic left ventricular function, and systolic left ventricular function were assessed echocardiographically. During 4.5±2.0 years of follow-up, the occurrence of (*1*) decompensated heart failure or all-cause mortality and (*2*) atherosclerotic events or all-cause mortality was recorded. We assessed the association of NT-proBNP and echocardiographic parameters with outcome (using Cox models) and evaluated the increased discriminative value associated with the addition of echocardiographic parameters and NT-proBNP (using integrated discrimination improvement and net reclassification improvement).

Results During follow-up, 104 patients suffered decompensated heart failure or all-cause mortality, and 127 patents had atherosclerotic events or all-cause mortality. In univariable analyses, NT-proBNP and echocardiographic parameters predicted cardiovascular events. NT-proBNP remained an independent predictor for both end points in multivariate analysis, whereas left ventricular mass index, left atrial volume index, and diastolic left ventricular function did not. The addition of NT-proBNP on top of clinical and various echocardiographic variables was associated with improvements in reclassification for decompensated heart failure or all-cause mortality (integrated discrimination improvement =6.5%–8.3%; net reclassification improvement =23.1%–27.0%; all $P \leq 0.03$). Adding echocardiographic variables on top of clinical variables and NT-proBNP was not associated with significant net reclassification improvement (all $P > 0.05$).

Conclusions Our data confirm NT-proBNP is an independent predictor of adverse outcomes in patients with CKD. The additional use of echocardiography for improvement of risk stratification is not supported by our results.

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Introduction

Patients with CKD experience severe reductions in quality of life and life expectancy, which are particularly driven by a high toll of cardiovascular (CV) events (1). Furthermore, health care costs are way out of proportion for the size of this patient population (2). Bearing these high human and societal costs in mind, better risk stratification is of considerable interest for targeted implementation of preventive therapies.

In recent years, plasma biomarkers—particularly natriuretic peptides—and imaging studies—particularly echocardiographic examinations—have been suggested to identify patients at high CV risk. Natriuretic peptides are independently associated with prevalent cardiovascular disease (CVD) and future CV events in cross–sectional (3,4) and prospective (5–8) CKD cohort studies. In echocardiographic studies, left ventricular (LV) hypertrophy (9–11) and left atrial enlargement (10,12–16) as well as systolic LV (10,17) and diastolic dysfunction (18,19) predicted adverse outcome among patients with CKD.

Of note, echocardiography has shortcomings, and screening of all patients with CKD seems unrealistic. Thus, cardiac plasma biomarkers may be attractive alternatives for CV outcome prediction in patients with CKD.

Prospective studies that simultaneously evaluated echocardiographic parameters and plasma biomarkers among patients with CKD are largely outstanding. Within the prospective Cardiovascular and Renal Outcome in CKD 2–4 Patients—The Fourth Homburg Evaluation (CARE FOR HOMe) Study, we aimed to analyze whether echocardiography and natriuretic peptides provide complementary or overlapping predictive information on CV outcome and whether one method might be dispensable.

Materials and Methods

Study Participants

The ongoing CARE for HOMe Study recruits patients with CKD G2–G4 (eGFR between 15 and 89 ml/min per 1.73 m^2 using the four–variable Modification of Diet in Renal Disease equation) (20).

The study was approved by the ethics committee in Saarbrücken and conducted in concordance with the Helsinki Declaration; all participants signed their written informed consent.

These analyses comprise 496 of 544 patients recruited between 2008 and 2015 who had an echocardiographic examination at study baseline. For technical reasons (unavailability of the operator), the remaining 48 patients had no baseline echocardiography.

Exclusion criteria of the CARE FOR HOMe Study were intake of systemic immune suppressive medication, HIV infection, acute infectious disease (arbitrarily defined as C–reactive protein levels >50 mg/L and/or need for requiring systemic antibiotic therapy), active cancer disease, RRT, AKI (defined as increase of plasma creatinine >50% within 4 weeks), pregnancy, and age <18 years old.

Baseline Examination

At baseline, fasting blood samples were drawn under standardized conditions after 5 minutes of rest. On the same day, plasma levels of amino–terminal probrain natriuretic peptide (NT-proBNP) were measured by a single laboratory using an electrochemiluminescence immunoassay (Cobas System; Elecsys 2010 proBNP II; Roche Diagnostics, Indianapolis, IN; intra–assay coefficient of variation =1.2%–1.9%; interassay coefficient of variation =1.7%–3.1%). Plasma levels of creatinine (traceable to isotope dilution-mass spectrometry), cystatin C, C-reactive protein, and total cholesterol were measured using standard methods.

Echocardiography Measurements

A single operator with long-time expertise in echocardiography performed and analyzed echocardiographic studies according to guidelines endorsed by the American Society of Echocardiography (ASE) (21).

Measurements were done from standard parasternal and apical views using a Sequoia C512 Ultrasound Unit (Acuson, Thousand Oaks, CA) with a linear probe (model 3V2c; 2–3 MHz).

Left ventricular mass index (LVMI) and left atrial volume index (LAVI) were determined by using the formula suggested by the ASE guidelines (21).

As a parameter of diastolic LV function, we calculated diastolic left ventricular function (E/e′) as the ratio of early diastolic mitral inflow velocity (E; assessed with pulsed wave Doppler ultrasound) to early diastolic septal mitral annular velocity (e′; assessed with tissue Doppler recording).

Systolic LV function was assessed as endocardial fractional shortening (FS) and by visual inspection. In general, we considered FS<28% as impaired LV function. We did not measure ejection fraction.

Outcome

For these analyses, all patients were followed until December of 2015 for CV events. Patients were not censored on initiation of RRT to avoid informative censoring, which could result in bias because of competing risks (22–24). The two predefined primary CV outcomes were (*1*) hospitalization for decompensated heart failure/all-cause mortality (HF/ACM) and (*2*) occurrence of an atherosclerotic event/all-cause mortality (AE/ACM).

Heart failure decompensation was defined as admission for a clinical syndrome involving symptoms (progressive dyspnea) in conjunction with clinical (peripheral edema or pulmonary rales) and/or radiologic (cardiomegaly, pulmonary edema, or pleural effusions) signs.

Atherosclerotic events were defined as acute myocardial infarction, surgical or interventional coronary/cerebrovascular/peripheral arterial revascularization, stroke, and amputation above the ankle.

Stroke was defined as a syndrome of "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting >24 hours or leading to death, with no apparent cause other than of vascular origin" following the World Health Organization definition (25).

Myocardial infarction was defined in accordance to the "Third universal definition of myocardial infarction" (26).

For assessment of incident CV events, all patients are invited annually for follow-up visits. In case of inability or unwillingness to follow this invitation, we contact patients or their next of kin for a telephone interview. Similarly, patients who have reached ESRD were contacted for annual telephone interviews.

All events reported by study participants or their next of kin were verified by medical records from the treating physicians. Two physicians blinded to echocardiographic and laboratory data adjudicated all events. In the case of disagreement, a third investigator was involved to make a final decision.

Additional information on baseline examinations and echocardiographic studies is given in Supplemental Material.

Statistical Analyses

Categorical variables are presented as a percentage of participants and compared using a Fisher exact test. Continuous data are expressed as means±SD or medians (interquartile ranges) if distribution was skewed and compared using a *t* test or a nonparametric Mann–Whitney test for independent samples. Correlation analyses were performed using Spearman coefficients. We additionally calculated Spearman partial correlation of NT-proBNP with echocardiographic parameters controlling for eGFR.

We calculated survival probabilities using the Kaplan–Meier method plotted in survival graphs and compared using the log rank test.

Univariable and multivariable Cox models were used to assess the associations between echocardiographic parameters (LVMI, LAVI, E/e′, and systolic LV function), NT-proBNP, and outcome rates. Different models were tested: model 1 was univariable analyses; model 2 included age and sex; model 3 included age, sex, eGFR, diabetes mellitus, prevalent CVD, smoking, diastolic BP, and cholesterol; and model 4 included variables of model 3 and NT-proBNP (for all analyses with echocardiographic parameters as exposure variables) or echocardiographic measurements (for analyses with NT-proBNP as exposure variable). To avoid overadjustment, we first decided to include a single echocardiographic parameter into the latter model (systolic LV function as the strongest echocardiographic parameter) but included the other echocardiographic parameters in a secondary exploratory Cox regression analysis. Echocardiographic parameters and logarithmized (with base 10; log) NT-proBNP were considered in Cox models as continuous linear variables and then, categorized into tertiles. Proportional hazards assumptions for exposure variables of interest were assessed using interaction with time quantification in time–dependent Cox modeling and visually assessed by plotting the $\log(-\log(S(t)))$ function as a function of survival time (t), where $S(t)$ represents the survival function.

As previously used by members of our group (27,28), the increased discriminative value associated with the addition of NT-proBNP and echocardiographic variables on top of the aforementioned covariates was evaluated using integrated discrimination improvement (IDI) and net reclassification improvement (NRI) (29). This method assesses the ability of a new model to reclassify subjects with and without a clinical event during follow-up. The ability of the new model to reclassify is summarized by the NRI statistic. The continuous NRI method developed by Uno *et al.* (29) was performed using R software (The R Foundation for Statistical Computing). The continuous NRI method does not require a prior definition of strata risk, thus considering the change in the estimation prediction as a continuous variable.

A two–sided P value <0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS statistics software (IBM SPSS, Chicago, IL) and the R software.

Results

Baseline Characteristics

The 496 CARE for HOMe Study participants had a mean age of 65.0±12.4 years old and a mean eGFR of 46±16 ml/min per 1.73 m^2. More than one third of all patients had prevalent diabetes mellitus, and 32% had prevalent CVD at study initiation. Median NT-proBNP was 211 (interquartile range, 90–602) pg/ml. Additional baseline characteristics are described in Table 1.

When stratifying patients into tertiles of NT-proBNP, patients with higher NT-proBNP levels were more likely to have prevalent CVD and impaired systolic LV function; moreover, they had worse renal function and higher measurements of LVMI, LAVI, and E/e′. Expectedly, patients with the highest NT-proBNP levels received β-blockers and diuretics more often than patients with the lowest NT-proBNP levels, whereas the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (which were often prescribed as nephroprotective rather than cardioprotective medication among the CARE for HOMe Study participants) differed less overtly (Supplemental Table 1).

Correlations between NT-proBNP and Other Baseline Variables

NT-proBNP was poorly or mildly correlated with higher age, albuminuria, systolic BP, lower eGFR, higher parathyroid hormone, and echocardiographic parameters (Table 2). Only eGFR and LAVI had absolute correlations ≥0.5 with NT-proBNP. The absolute correlation between NT-proBNP and echocardiographic variables after adjustment for eGFR remained <0.60, and the highest partial correlation was observed for LAVI (0.54) (Supplemental Table 2).

Survival Analyses

Vital status was known for all patients at the end of the follow-up in December of 2015. Three of 496 patients withdrew their consent for CV event recording and subsequently, were considered as lost to follow-up.

During 4.5±2.0 years of follow-up, 104 patients suffered HF/ACM, whereas 127 patients suffered AE/ACM (details are in Supplemental Material).

In Kaplan–Meier analysis, patients with highest NT-proBNP, highest LVMI, highest LAVI, and highest E/e′ were all at highest risks for HF/ACM (Figure 1) and AE/ACM (Figure 2). Similarly, patients with impaired systolic LV function had higher risks for HF/ACM (Figure 1) and AE/ACM (Figure 2) than patients with intact systolic LV function.

Accordingly, in univariable Cox regression analysis, both HF/ACM and AE/ACM were predicted by higher levels of log NT-proBNP, higher LVMI, higher LAVI, and higher E/e′ when each was considered as a continuous variable (Tables 3 and 4).

Log NT-proBNP levels, LVMI, LAVI, and E/e′ remained predictors of adverse outcome after adjustment for age and sex (model 2) and additional adjustment for eGFR, diabetes mellitus, prevalent CVD, smoking, diastolic BP, and cholesterol (model 3). Finally, NT-proBNP remained strongly and significantly associated with HF/ACM and AE/ACM after adjustment for systolic LV function. In contrast, LVMI, LAVI, and E/e′ were no longer significant predictors of HF/ACM after adjustment for NT-proBNP, and neither LVMI nor LAVI predicted AE/ACM in the fully adjusted model.

In exploratory analyses, we considered NT-proBNP, LVMI, LAVI, E/e′, and systolic LV function as categorized variables.

Patients in the highest tertile of NT-proBNP had a 19.11-fold higher risk (95% confidence interval [95% CI], 7.74 to 47.18) for HF/ACM in univariable analyses and a 7.07-fold higher risk (95% CI, 2.66 to 18.81) in the fully adjusted model, including adjustment for systolic LV function. The risk for AE/ACM was similarly increased, with an 8.16-fold higher risk (95% CI, 4.55 to 14.64) in the unadjusted model and a 3.64-fold higher risk (95% CI, 1.84 to 7.19) in the final model.

Table 1. Baseline characteristics of study participants

Variable	Total Cohort, *n*=496	No HF/ACM, *n*=392	HF/ACM, *n*=104	*P* Value	No AE/ACM, *n*=369	AE/ACM, *n*=127	*P* Value
Age, yr	65.0±12.4	63.0±12.5	72.5±8.8	<0.001	63.2±12.7	70.4±9.8	<0.001
Sex, women	205 (41%)	171 (44%)	34 (33%)	0.04	167 (45%)	38 (30%)	0.002
Prevalent CVD	160 (32%)	106 (27%)	54 (52%)	<0.001	86 (23%)	74 (58%)	<0.001
BMI, kg/m^2	30.4±5.5	30.4±5.5	30.3±5.5	0.83	30.6±5.6	29.7±5.2	0.13
Diabetes mellitus	188 (38%)	133 (34%)	55 (53%)	<0.001	122 (33%)	66 (52%)	<0.001
Current nicotine	54 (11%)	48 (12%)	6 (6%)	0.08	41 (11%)	13 (10%)	0.87
Cholesterol, mg/dl	192±43	194±43	183±42	0.01	196±43	180±41	<0.001
NT-proBNP, pg/ml	211 (90–602)	152 (72–325)	964 (399–2353)	<0.001	146 (72–321)	690 (298–2157)	<0.001
CRP, mg/L	2.7 (1.2–5.0)	2.5 (1.1–4.6)	3.8 (1.6–7.9)	0.002	2.4 (1.1–4.5)	3.8 (1.6–8.4)	<0.001
Phosphorus, mg/dl	3.37±0.68	3.28±0.61	3.71±0.82	<0.001	3.32±0.62	3.52±0.82	0.003
Parathyroid hormone, pg/ml	52 (37–82)	47 (35–68)	82 (53–126)	<0.001	48 (35–69)	70 (42–112)	<0.001
eGFR, ml/min per 1.73 m^2	46±16	49±15	35±12	<0.001	49±16	38±14	<0.001
CKD stage				<0.001			<0.001
G2	103 (21%)	98 (25%)	5 (5%)		95 (26%)	8 (6%)	
G3a	169 (34%)	154 (39%)	15 (14%)		139 (38%)	30 (24%)	
G3b	137 (28%)	91 (23%)	46 (44%)		86 (23%)	51 (40%)	
G4	87 (18%)	49 (12%)	38 (37%)		49 (13%)	38 (30%)	
Albuminuria, mg/g creatinine	32 (7–201)	24 (6–171)	87 (25–266)	<0.001	22 (6–147)	80 (24–306)	<0.001
Systolic BP, mmHg	152±24	152±23	155±26	0.20	152±23	155±26	0.16
Diastolic BP, mmHg	86±13	87±13	81±12	<0.001	86±13	83±13	<0.01
ACE inhibitors	171 (34%)	132 (34%)	39 (38%)	0.49	115 (31%)	56 (44%)	<0.01
Angiotensin receptor blockers	251 (51%)	207 (53%)	44 (42%)	0.06	203 (55%)	48 (38%)	<0.001
Aldosterone receptor blocker	111 (22%)	85 (22%)	26 (25%)	0.51	83 (23%)	28 (22%)	>0.99
β-Blockers	341 (69%)	255 (65%)	86 (83%)	<0.001	241 (65%)	100 (79%)	<0.01
Loop diuretics	216 (43%)	138 (35%)	78 (75%)	<0.001	136 (37%)	80 (63%)	<0.001
Thiazide/thiazide-like diuretics	254 (51%)	202 (52%)	52 (50%)	0.83	192 (52%)	62 (49%)	0.54
Statins	254 (51%)	196 (50%)	58 (56%)	0.32	179 (49%)	75 (59%)	0.05
LVMI, g/m^2	92.8±28.0	89.3±25.4	106.7±32.7	<0.001	88.8±25.4	105.1±31.8	<0.001
E/e′	8.9±3.3	8.4±3.0	10.8±3.8	<0.001	8.3±3.0	10.6±3.7	<0.001
LAVI, ml/m^2	37.9±12.9	35.8±11.5	46.0±14.7	<0.001	35.8±11.4	44.2±15.0	<0.001
Impaired systolic LV function	65 (13%)	31 (8%)	34 (33%)	<0.001	33 (9%)	32 (25%)	<0.001

Data are presented as means±SD or medians (interquartile ranges) for continuous variables and numbers of patients (percentages) for categorical variables. *P* values correspond to the comparison of patients characteristics according to the end point. AE/ACM, end point atherosclerotic events/all-cause mortality; HF/ACM, end point decompensated heart failure/all-cause mortality; CVD, cardiovascular disease; BMI, body mass index; NT-proBNP, amino–terminal probrain natriuretic peptide; CRP, C-reactive protein; ACE, angiotensin-converting enzyme; LVMI, left ventricular mass index; E/e′, diastolic left ventricular function; LAVI, left atrial volume index; LV, left ventricular.

Table 2. Univariable Spearman correlation coefficients

Variable	NT-proBNP, pg/ml	
	Rho	*P* Value
Age, yr	0.45	<0.001
BMI, kg/m^2	−0.03	0.46
Cholesterol, mg/dl	−0.11	0.01
CRP, mg/L	0.16	<0.001
Phosphorus, mg/dl	0.25	<0.001
Parathyroid hormone, pg/ml	0.40	<0.001
eGFR, ml/min per 1.73 m^2	−0.55	<0.001
Albuminuria, mg/g creatinine	0.26	<0.001
Systolic BP, mmHg	0.15	<0.001
Diastolic BP, mmHg	−0.18	<0.001
LVMI, g/m^2	0.35	<0.001
LAVI, ml/m^2	0.56	<0.001
E/e′	0.45	<0.001

NT-proBNP, amino–terminal probrain natriuretic peptide; BMI, body mass index; CRP, C-reactive protein; LVMI, left ventricular mass index; LAVI, left atrial volume index; E/e′, diastolic left ventricular function.

Patients in the highest tertile of LVMI, LAVI, and E/e′ had significantly higher rates of HF/ACM and AE/ACM at univariable analyses, which however, did not persist after adjustment for clinical confounders and NT-proBNP (Tables 3 and 4). Patients with impaired systolic LV function had higher risk of HF/ACM (hazard ratio, 2.52; 95% CI, 1.61 to 3.94) but not higher risk of AE/ACM (hazard ratio, 1.36; 95% CI, 0.88 to 2.09) after adjustment for clinical confounders and NT-proBNP.

When including all echocardiographic variables in conjunction with clinical parameters and NT-proBNP into one single Cox regression analysis, NT-proBNP independently predicted both CV end points, whereas echocardiographic parameters did not (Supplemental Table 3).

Improvement in Reclassification Associated with NT-proBNP and Echocardiographic Variables

The addition of NT-proBNP into the survival model on top of clinical variables was associated with a significant improvement in reclassification for the end point HF/ACM (IDI=11.9%; $P<0.001$; continuous NRI=33.8%; $P<0.001$) (Supplemental Figure 1). The addition of NT-proBNP into the survival model on top of clinical variables and various echocardiographic variables was associated with significant improvements in reclassification ranging from 6.5% to 8.3% of IDI and from 23.1% to 27.0% of NRI (all $P\leq0.03$) (Supplemental Figure 1). In contrast, adding echocardiographic variables on top of clinical variables and NT-proBNP was not associated with significant improvements in NRI ($P>0.10$). A similar pattern was observed for the end point AE/ACM (Supplemental Figure 2).

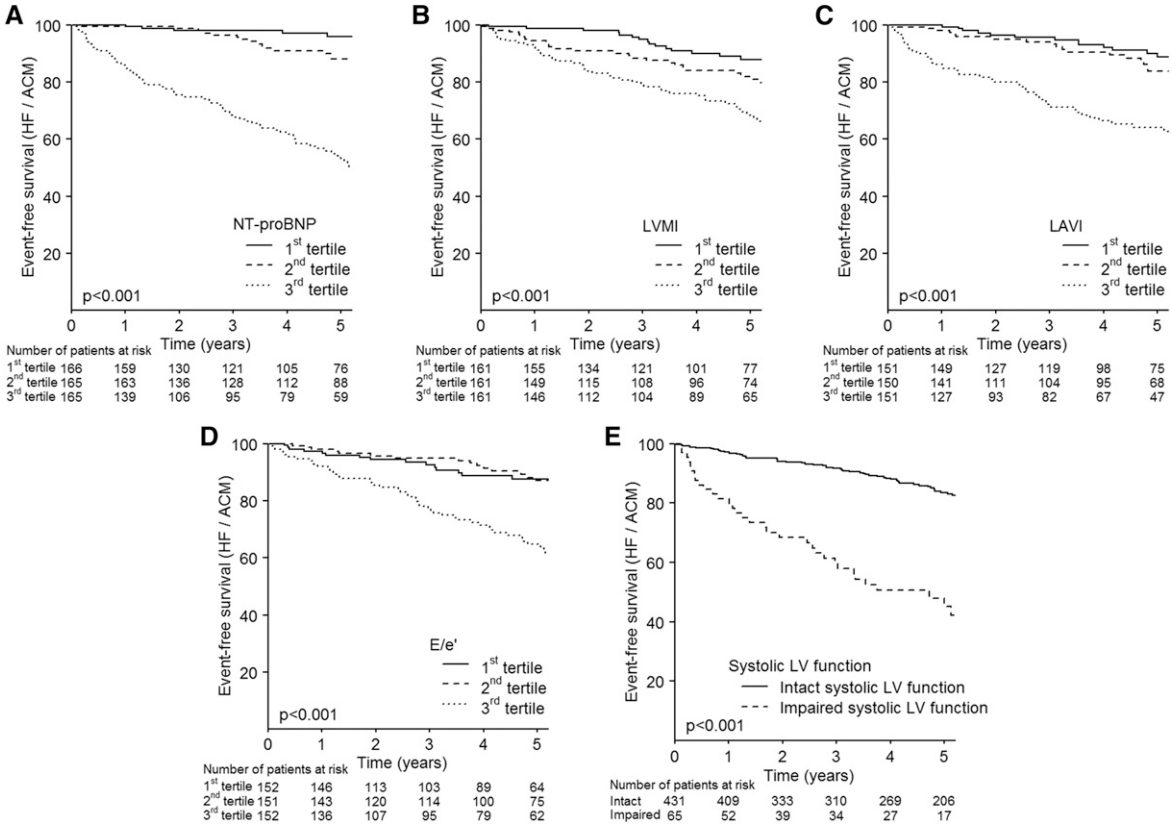

Figure 1. | Kaplan–Meier analyses with subsequent log rank test (end point decompensated heart failure/all-cause mortality [HF/ACM]). Event-free survival in patients with CKD stratified by (A) tertiles of amino–terminal probrain natriuretic peptide (NT-proBNP), (B) tertiles of left ventricular mass index (LVMI), (C) tertiles of left atrial volume index (LAVI), (D) tertiles of diastolic left ventricular function (E/e′), and (E) intact and impaired systolic left ventricular (LV) function.

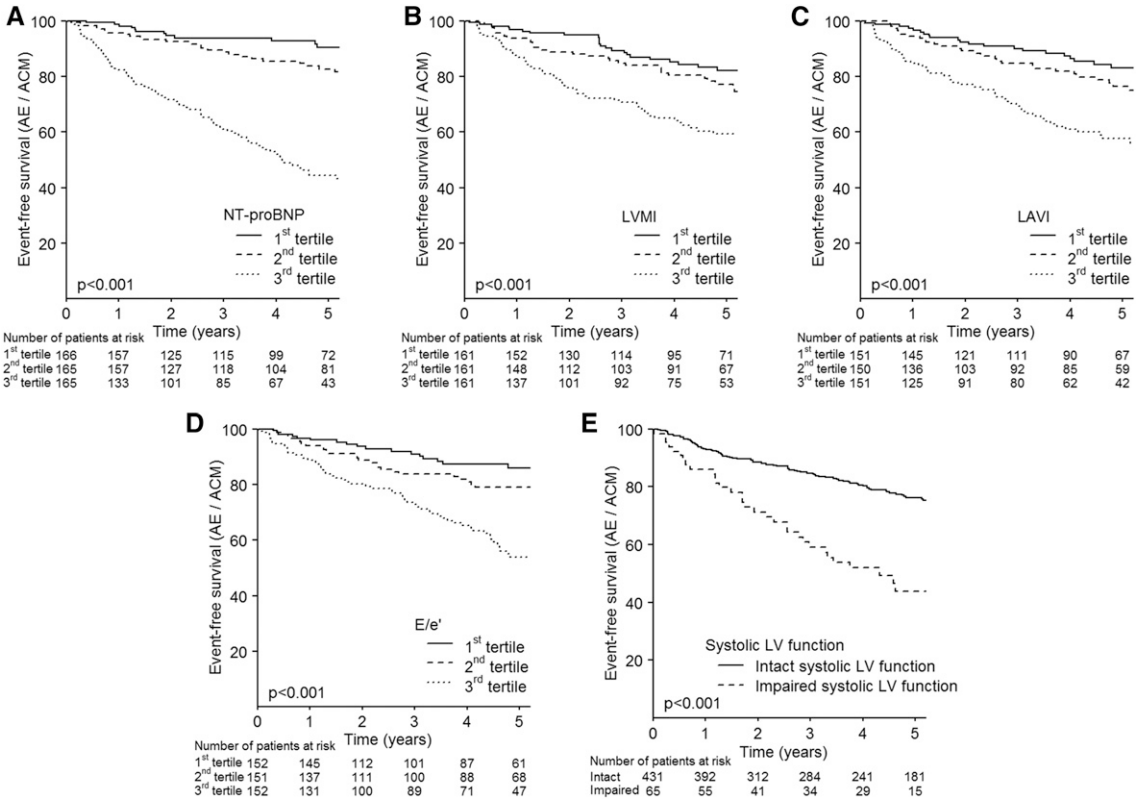

Figure 2. | **Kaplan–Meier analyses with subsequent log rank test (end point atherosclerotic events/all-cause mortality [AE/ACM]).** Event-free survival in patients with CKD stratified by (A) tertiles of amino–terminal probrain natriuretic peptide (NT-proBNP), (B) tertiles of left ventricular mass index (LVMI), (C) tertiles of left atrial volume index (LAVI), (D) tertiles of diastolic left ventricular function (E/e'), and (E) intact and impaired systolic left ventricular (LV) function.

Discussion

Among 496 patients with CKD not on dialysis, we analyzed whether NT-proBNP and echocardiographic parameters provide complementary or redundant information on future CV events.

We first confirmed that echocardiographic parameters predict adverse CV outcome in both univariable analyses and after adjustment for conventional CV factors and renal function. These findings are in line with prior studies that measured LAVI, LVMI, systolic LV, and/or diastolic function among patients with CKD not on dialysis (9–11,19). Of note, these studies did not adjust for natriuretic peptides.

Next, in accordance with other recent prospective cohort studies, we confirmed NT-proBNP as a strong predictor of CV outcome among patients with CKD not on dialysis (6–8). We illustrated that NT-proBNP remains a strong outcome predictor even after full adjustment for potential confounders, particularly for eGFR. This finding is notable, because it has been argued before (5,30) that the strong correlation between NT-proBNP and GFR—resulting from decreased renal elimination of NT-proBNP in advanced CKD—may preclude the use of this plasma biomarker as an independent CV outcome marker in CKD.

Aggregating our findings on echocardiographic parameters and plasma biomarkers, we conclude that echocardiography and NT-proBNP provide redundant rather than complementary predictive information: LVMI, LAVI, and E/e' did not remain independent CV outcome predictors after adjustment for NT-proBNP. Impaired systolic LV function predicted heart failure but not atherosclerotic events in the fully adjusted Cox models. *Vice versa*, the predictive power of NT-proBNP was only moderately affected by adjustment for echocardiographic parameters. Hence, we conclude that NT-proBNP is a superior predictor of CV events.

We hypothesize that—compared with a clinical cohort study with a single observer and highly standardized echocardiographic examinations—a real world setting will further dilute the strength of echocardiographic parameters for CV outcome prediction. In clinical routine, echocardiography is performed by numerous physicians and technicians with different skills on diverse ultrasound machines, often with time constraints, which will cause substantial interobserver variability. However, even in clinical study settings, echocardiographic measurements are prone to substantial imprecision (31,32). In contrast, NT-proBNP measurements have been standardized across different laboratories in recent years, and intraindividual fluctuations are largely caused by underlying pathophysiologic factors rather than measurement variability (33).

Additional aspects support a plasma biomarker- over an echocardiography-based approach for CV outcome prediction in clinical practice. First, NT-proBNP measurements are substantially less time and resource consuming

Table 3. Cox models (end point decompensated heart failure/all-cause mortality)

Exposure Variable	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Continuous predictors								
Log NT-proBNP, pg/ml	6.63 (4.85 to 9.07)	<0.001	5.25 (3.74 to 7.38)	<0.001	4.36 (2.94 to 6.46)	<0.001	3.61 (2.35 to 5.54)	<0.001
LVMI, g/m^2	1.01 (1.01 to 1.02)	<0.001	1.01 (1.00 to 1.02)	<0.001	1.01 (1.00 to 1.01)	<0.01	1.00 (0.99 to 1.00)	0.57
LAVI, ml/m^2	1.05 (1.04 to 1.07)	<0.001	1.04 (1.03 to 1.06)	<0.001	1.03 (1.01 to 1.04)	<0.001	1.00 (0.99 to 1.02)	0.73
E/e′	1.15 (1.10 to 1.20)	<0.001	1.13 (1.07 to 1.19)	<0.001	1.07 (1.01 to 1.13)	0.02	0.99 (0.94 to 1.05)	0.82
Categorized predictors								
NT-proBNP		<0.001		<0.001		<0.001		<0.001
Second tertile[a]	3.49 (1.30 to 9.34)	0.01	2.49 (0.91 to 6.76)	0.07	2.15 (0.79 to 5.88)	0.13	2.09 (0.77 to 5.69)	0.15
Third tertile[a]	19.11 (7.74 to 47.18)	<0.001	11.34 (4.47 to 28.76)	<0.001	8.20 (3.11 to 21.60)	<0.001	7.07 (2.66 to 18.81)	<0.001
LVMI		0.001		0.06		0.11		0.98
Second tertile[a]	1.58 (0.89 to 2.82)	0.12	1.20 (0.66 to 2.17)	0.54	1.22 (0.67 to 2.20)	0.52	1.05 (0.58 to 1.90)	0.88
Third tertile[a]	2.90 (1.71 to 4.92)	<0.001	1.82 (1.04 to 3.17)	0.03	1.74 (0.99 to 3.07)	0.05	1.06 (0.59 to 1.90)	0.85
LAVI		<0.001		<0.001		0.001		0.12
Second tertile[a]	1.64 (0.86 to 3.15)	0.14	1.13 (0.58 to 2.20)	0.72	1.25 (0.64 to 2.43)	0.51	1.04 (0.52 to 2.06)	0.92
Third tertile[a]	4.61 (2.59 to 8.20)	<0.001	2.77 (1.52 to 5.02)	<0.001	2.60 (1.42 to 4.73)	0.002	1.66 (0.88 to 3.13)	0.12
E/e′		<0.001		<0.001		0.01		0.08
Second tertile[a]	1.02 (0.53 to 1.97)	0.95	0.82 (0.43 to 1.59)	0.56	0.73 (0.37 to 1.44)	0.37	0.66 (0.34 to 1.31)	0.24
Third tertile[a]	3.60 (2.08 to 6.22)	<0.001	2.28 (1.28 to 4.04)	<0.01	1.64 (0.91 to 2.98)	0.10	1.26 (0.69 to 2.32)	0.45
Systolic LV function								
Impaired (versus normal)	4.62 (3.05 to 6.98)	<0.001	3.51 (2.30 to 5.34)	<0.001	3.31 (2.12 to 5.17)	<0.001	2.52 (1.61 to 3.94)	<0.001

Model 1 is the univariable analysis. Model 2 is adjusted for age and sex. Model 3 is adjusted for age, sex, eGFR, diabetes mellitus, prevalent cardiovascular disease, smoking, diastolic BP, and cholesterol. Model 4 includes variables from model 3 and NT-proBNP (for all analyses with echocardiographic parameters as exposure variable) or systolic LV function (analyses with NT-proBNP as exposure variable). HR, hazard ratio; 95% CI, 95% confidence interval; NT-proBNP, amino–terminal probrain natriuretic peptide; LVMI, left ventricular mass index; LAVI, left atrial volume index; E/e′, diastolic left ventricular function.

[a]Reference is the first tertile.

Table 4. Cox models (end point atherosclerotic event/all-cause mortality)

Exposure Variable	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Continuous predictors								
Log NT-proBNP, pg/ml	4.39 (3.36 to 5.74)	<0.001	3.68 (2.77 to 4.90)	<0.001	2.88 (2.05 to 4.04)	<0.001	2.91 (1.99 to 4.25)	<0.001
LVMI, g/m^2	1.01 (1.01 to 1.02)	<0.001	1.01 (1.01 to 1.02)	<0.001	1.01 (1.00 to 1.01)	0.02	1.00 (1.00 to 1.01)	0.74
LAVI, ml/m^2	1.05 (1.03 to 1.06)	<0.001	1.03 (1.02 to 1.05)	<0.001	1.03 (1.01 to 1.04)	<0.001	1.01 (0.99 to 1.03)	0.31
E/e′	1.16 (1.11 to 1.21)	<0.001	1.17 (1.11 to 1.24)	<0.001	1.12 (1.05 to 1.19)	<0.001	1.08 (1.01 to 1.14)	0.02
Categorized predictors								
NT-proBNP		<0.001		<0.001		<0.001		<0.001
Second tertile[a]	2.11 (1.10 to 4.07)	0.02	1.78 (0.91 to 3.48)	0.09	1.76 (0.89 to 3.46)	0.10	1.70 (0.86 to 3.37)	0.12
Third tertile[a]	8.16 (4.55 to 14.64)	<0.001	5.90 (3.17 to 10.98)	<0.001	3.96 (2.03 to 7.72)	<0.001	3.64 (1.84 to 7.19)	<0.001
LVMI		<0.001		<0.01		0.07		0.38
Second tertile[a]	1.39 (0.83 to 2.33)	0.22	1.05 (0.61 to 1.78)	0.87	0.95 (0.56 to 1.62)	0.86	0.86 (0.51 to 1.48)	0.59
Third tertile[a]	2.82 (1.77 to 4.50)	<0.001	1.89 (1.16 to 3.09)	0.01	1.52 (0.92 to 2.51)	0.10	1.18 (0.71 to 1.98)	0.52
LAVI		<0.001		0.003		0.02		0.27
Second tertile[a]	1.53 (0.88 to 2.64)	0.13	1.21 (0.69 to 2.12)	0.50	1.23 (0.71 to 2.15)	0.46	1.10 (0.62 to 1.95)	0.74
Third tertile[a]	3.28 (2.00 to 5.37)	<0.001	2.18 (1.30 to 3.65)	0.003	1.95 (1.17 to 3.25)	0.01	1.48 (0.86 to 2.54)	0.16
E/e′		<0.001		<0.001		0.05		0.29
Second tertile[a]	1.43 (0.81 to 2.53)	0.22	1.24 (0.70 to 2.20)	0.47	1.00 (0.56 to 1.81)	0.99	0.95 (0.52 to 1.71)	0.85
Third tertile[a]	3.43 (2.07 to 5.71)	<0.001	2.54 (1.49 to 4.34)	<0.001	1.66 (0.97 to 2.84)	0.06	1.34 (0.78 to 2.31)	0.30
Systolic LV function								
Impaired (versus normal)	2.70 (1.80 to 4.03)	<0.001	2.02 (1.34 to 3.05)	<0.001	1.75 (1.15 to 2.68)	<0.01	1.36 (0.88 to 2.09)	0.17

Model 1 is the univariable analysis. Model 2 is adjusted for age and sex. Model 3 is adjusted for age, sex, eGFR, diabetes mellitus, prevalent cardiovascular disease, smoking, diastolic BP, and cholesterol. Model 4 includes variables from model 3 and NT-proBNP (for all analyses with echocardiographic parameters as exposure variable) or systolic LV function (analyses with NT-proBNP as exposure variable). HR, hazard ratio; 95% CI, 95% confidence interval; NT-proBNP, amino–terminal probrain natriuretic peptide; LVMI, left ventricular mass index; LAVI, left atrial volume index; E/e′, diastolic left ventricular function.

[a]Reference is the first tertile.

than echocardiographic studies (34). Second, few data from prospective interventional trials are available on therapeutic consequences of screening echocardiography among individuals with or without CKD. In contrast, beyond the field of nephrology, NT-proBNP–guided cardioprotective treatment strategies have been implemented in recent years after several interventional trials proved their superiority over clinical guided treatment strategies in both primary and secondary prevention (35–38).

Against this background, the American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure suggested an NT-proBNP–guided treatment strategy for optimization of cardioprotective therapy (39) but disfavored routine repeated echocardiography in stable patients. Of importance, the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment Study is designed to definitively assess the effects of an NT-proBNP–guided strategy in high-risk patients with systolic heart failure on clinically relevant end points of mortality, hospitalization, quality of life, and medical resource use (40). Admittedly, it remains to be determined in separate studies whether such an approach can successfully be transferred to patients with CKD with high NT-proBNP who do not consistently have a typical pattern of signs and symptoms that defines heart failure clinically. Moreover, hypervolemia may affect NT-proBNP measurements in routine clinical practice more frequently than among study patients, in whom intensive nephrologic care with close titration of diuretics and fluid intake may prevent substantial volume overload.

Our study has several limitations. First, we included patients with and without CVD at study initiation. We cannot exclude the possibility that CV event prediction might differ between these two patient groups. Second, we applied a limited number of conventional echocardiographic measurements. We particularly focused on parameters that, in clinical practice, are assessed during a standardized echocardiographic examination (21). We are positive that this strategy improves clinical usability of our study and allows better comparability with earlier studies in the field of CKD, which also focused on left atrial size (10,12–16), LV hypertrophy (9–11), and conventional measures of LV functions (10,17–19). Instead, we did not collect data on novel techniques (*e.g.*, strain analyses); for assessment of systolic LV function, we used endocardial FS rather than biplane ejection fraction. Third, although outcome data were adjudicated by physicians blinded to baseline data, treating nephrologists were not blinded to baseline NT-proBNP and echocardiographic measurements, which may have affected routine nephrologic care.

As study strengths, the CARE for HOMe Study is a contemporary cohort of patients with CKD with a broad spectrum of primary kidney diseases. We provide data from echocardiographic studies performed by a single observer with long-term expertise in echocardiography on one single ultrasound unit. Clinical outcome data were adjudicated by two independent physicians who had full access to all original medical records. Accuracy of outcome data was further strengthened by inviting all patients to annual follow-up visits.

In summary, the CARE for HOMe Study first confirms that both NT-proBNP and several echocardiographic parameters are univariable predictors of adverse CV outcome in patients with mild to moderate CKD. Second, we show that, in adjusted multivariable analyses, NT-proBNP outperforms echocardiographic parameters as a predictor of adverse CV outcome. Given that laboratory measurement of NT-proBNP is less cumbersome and less time consuming than a standard echocardiographic study, the CARE for HOMe Study suggests against routine echocardiographic studies in patients with CKD for assessment of future CV risk.

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Disclosures

None.

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