

# 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 patients 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.

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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<sup>2</sup> 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  $65.0 \pm 12.4$  years old and a mean eGFR of  $46 \pm 16$  ml/min per  $1.73 \text{ m}^2$ . 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  $\beta$ -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  $\geq 0.5$  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  $4.5 \pm 2.0$  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 <sup>2</sup>	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 <sup>2</sup>	46±16	49±15	35±12	<0.001	49±16	38±14	<0.001
<b>CKD stage</b>				<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
LVMl, g/m <sup>2</sup>	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 <sup>2</sup>	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 pro-brain natriuretic peptide; CRP, C-reactive protein; ACE, angiotensin-converting enzyme; LVMl, 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 <sup>2</sup>	-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 <sup>2</sup>	-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 <sup>2</sup>	0.35	<0.001
LAVI, ml/m <sup>2</sup>	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.

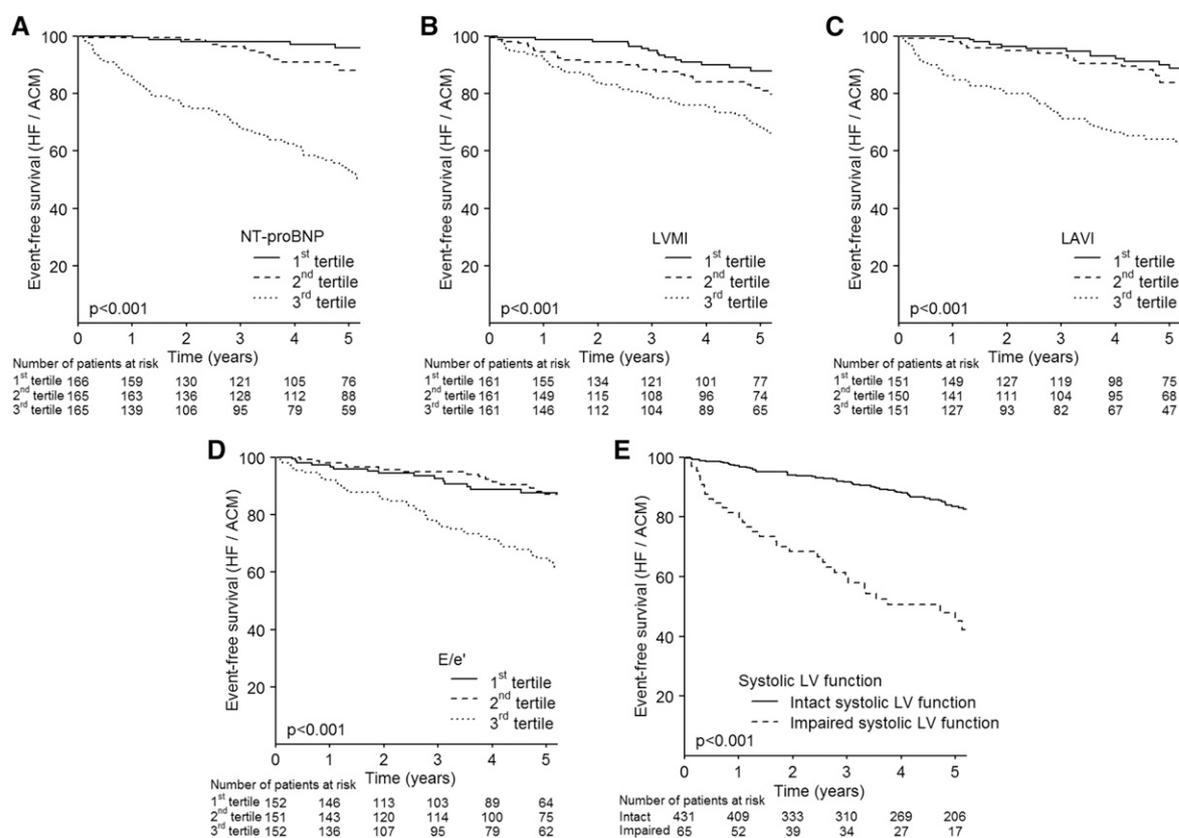
Patients in the highest tertile of LVMI, LAVI, and E/e' had significantly higher rates of HF/ACM and AE/ACM at univariable analyses, which however, did not persist after adjustment for clinical confounders and NT-proBNP

(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.

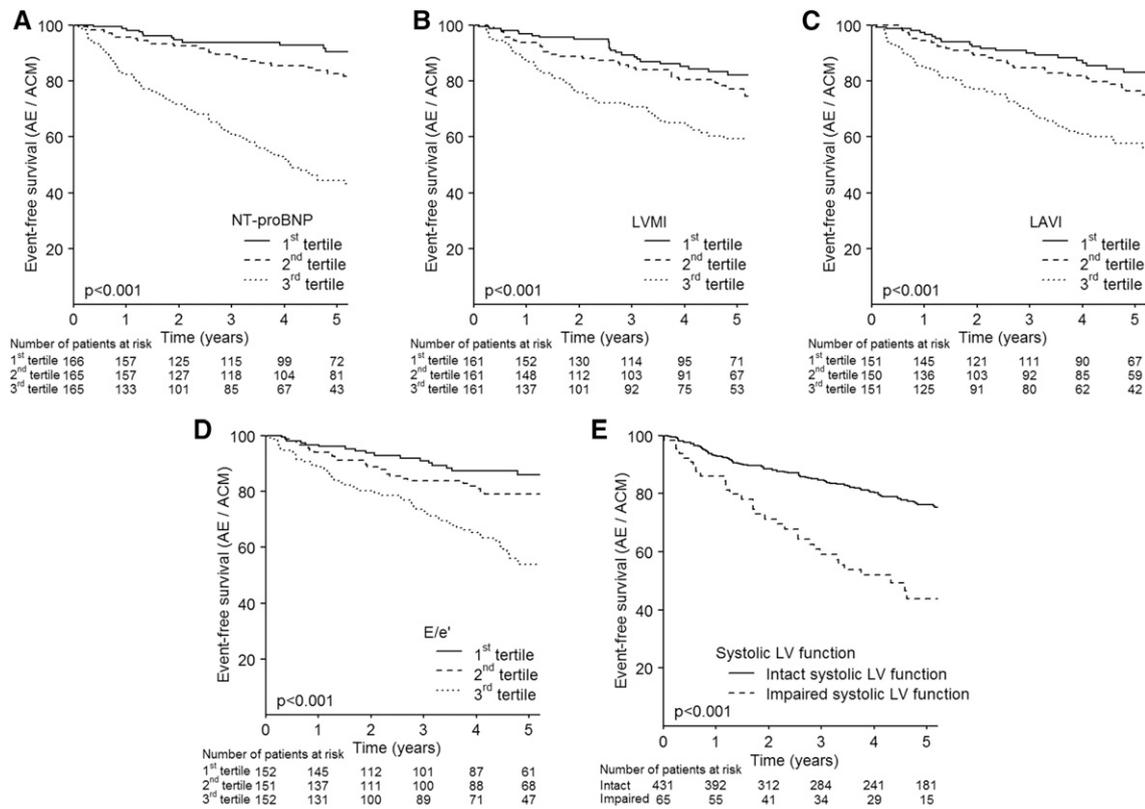
When including all echocardiographic variables in conjunction with clinical parameters and NT-proBNP into one single Cox regression analysis, NT-proBNP independently predicted both CV end points, whereas echocardiographic parameters did not (Supplemental Table 3).

### 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  $P\leq 0.03$ ) (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

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
<b>Continuous predictors</b>								
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 <sup>2</sup>	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 <sup>2</sup>	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
<b>Categorized predictors</b>								
NT-proBNP	3.49 (1.30 to 9.34)	<0.001	2.49 (0.91 to 6.76)	<0.001	2.15 (0.79 to 5.88)	<0.001	2.09 (0.77 to 5.69)	<0.001
Second tertile <sup>a</sup>	19.11 (7.74 to 47.18)	0.01	11.34 (4.47 to 28.76)	0.07	8.20 (3.11 to 21.60)	0.13	7.07 (2.66 to 18.81)	0.15
Third tertile <sup>a</sup>		<0.001		<0.001		<0.001		<0.001
LVMi	1.58 (0.89 to 2.82)	0.001	1.20 (0.66 to 2.17)	0.06	1.22 (0.67 to 2.20)	0.11	1.05 (0.58 to 1.90)	0.98
Second tertile <sup>a</sup>	2.90 (1.71 to 4.92)	0.12	1.82 (1.04 to 3.17)	0.54	1.74 (0.99 to 3.07)	0.52	1.06 (0.59 to 1.90)	0.88
Third tertile <sup>a</sup>		<0.001		0.03		0.05		0.85
LAVI	1.64 (0.86 to 3.15)	<0.001	1.13 (0.58 to 2.20)	<0.001	1.25 (0.64 to 2.43)	0.001	1.04 (0.52 to 2.06)	0.12
Second tertile <sup>a</sup>	4.61 (2.59 to 8.20)	0.14	2.77 (1.52 to 5.02)	0.72	2.60 (1.42 to 4.73)	0.51	1.66 (0.88 to 3.13)	0.92
Third tertile <sup>a</sup>		<0.001		<0.001		0.01		0.12
E/e'	1.02 (0.53 to 1.97)	<0.001	0.82 (0.43 to 1.59)	<0.001	0.73 (0.37 to 1.44)	0.01	0.66 (0.34 to 1.31)	0.08
Second tertile <sup>a</sup>	3.60 (2.08 to 6.22)	0.95	2.28 (1.28 to 4.04)	0.56	1.64 (0.91 to 2.98)	0.37	1.26 (0.69 to 2.32)	0.24
Third tertile <sup>a</sup>		<0.001		<0.01		0.10		0.45
Systolic LV function	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
Impaired (versus normal)								

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 pro-brain natriuretic peptide; LVMi, left ventricular mass index; LAVI, left atrial volume index; E/e', diastolic left ventricular function.

<sup>a</sup>Reference is the first tertile.

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
<b>Continuous predictors</b>								
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
LVMl, g/m <sup>2</sup>	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 <sup>2</sup>	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
<b>Categorized predictors</b>								
NT-proBNP		<0.001		<0.001		<0.001		<0.001
Second tertile <sup>a</sup>	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 <sup>a</sup>	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
LVMl		<0.001		<0.01		0.07		0.38
Second tertile <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	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		<0.001		<0.001		<0.001		<0.001
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)	<0.001	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; LVMl, left ventricular mass index; LAVI, left atrial volume index; E/e', diastolic left ventricular function.  
<sup>a</sup>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.

#### References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP: Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *Lancet* 382: 339–352, 2013
2. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW: Chronic kidney disease: Global dimension and perspectives. *Lancet* 382: 260–272, 2013
3. Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, Christenson R, deFilippi C, Chen J, He J, Kallam RR, Raj DS, Schelling JR, Wright J, Go AS, Shlipak MG; Chronic Renal Insufficiency Cohort Investigators: Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol* 111: 432–438, 2013
4. DeFilippi CR, Fink JC, Nass CM, Chen H, Christenson R: N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. *Am J Kidney Dis* 46: 35–44, 2005
5. Scheven L, de Jong PE, Hillege HL, Lambers Heerspink HJ, van Pelt LJ, Kootstra JE, Bakker SJ, Gansevoort RT; PREVEND study group: High-sensitive troponin T and N-terminal pro-B type natriuretic peptide are associated with cardiovascular events despite the cross-sectional association with albuminuria and glomerular filtration rate. *Eur Heart J* 33: 2272–2281, 2012
6. Matsushita K, Sang Y, Ballew SH, Astor BC, Hoogeveen RC, Solomon SD, Ballantyne CM, Woodward M, Coresh J: Cardiac and kidney markers for cardiovascular prediction in individuals with chronic kidney disease: The Atherosclerosis Risk in Communities study. *Arterioscler Thromb Vasc Biol* 34: 1770–1777, 2014
7. McMurray JJ, Uno H, Jarolim P, Desai AS, de Zeeuw D, Eckardt KU, Ivanovich P, Levey AS, Lewis EF, McGill JB, Parfrey P, Parving HH, Toto RM, Solomon SD, Pfeffer MA: Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: An analysis of the Trial to Reduce cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). *Am J Heart* 162: 748–755.e3, 2011
8. Bansal N, Hyre Anderson A, Yang W, Christenson RH, deFilippi CR, Deo R, Dries DL, Go AS, He J, Kusek JW, Lash JP, Raj D, Rosas S, Wolf M, Zhang X, Shlipak MG, Feldman HI: High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Soc Nephrol* 26: 946–956, 2015
9. Paoletti E, De Nicola L, Gabbai FB, Chiodini P, Ravera M, Pieracci L, Marre S, Cassottana P, Lucà S, Vettoretti S, Borrelli S, Conte G, Minutolo R: Associations of left ventricular hypertrophy and

- geometry with adverse outcomes in patients with CKD and hypertension. *Clin J Am Soc Nephrol* 11: 271–279, 2016
10. Chen SC, Chang JM, Liu WC, Huang JC, Tsai JC, Lin MY, Su HM, Hwang SJ, Chen HC: Echocardiographic parameters are independently associated with increased cardiovascular events in patients with chronic kidney disease. *Nephrol Dial Transplant* 27: 1064–1070, 2012
  11. Eckardt KU, Scherhag A, Macdougall IC, Tsakiris D, Clyne N, Locatelli F, Zaug MF, Burger HU, Druke TB: Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. *J Am Soc Nephrol* 20: 2651–2660, 2009
  12. Kim SJ, Han SH, Park JT, Kim JK, Oh HJ, Yoo DE, Yoo TH, Kang SW, Choi KH: Left atrial volume is an independent predictor of mortality in CAPD patients. *Nephrol Dial Transplant* 26: 3732–3739, 2011
  13. Shizuku J, Yamashita T, Ohba T, Kabaya T, Nitta K: Left atrial volume is an independent predictor of all-cause mortality in chronic hemodialysis patients. *Intern Med* 51: 1479–1485, 2012
  14. Patel RK, Jardine AG, Mark PB, Cunningham AF, Steedman T, Powell JR, McQuarrie EP, Stevens KK, Dargie HJ, Jardine AG: Association of left atrial volume with mortality among ESRD patients with left ventricular hypertrophy referred for kidney transplantation. *Am J Kidney Dis* 55: 1088–1096, 2010
  15. Hee L, Nguyen T, Whatmough M, Descallar J, Chen J, Kapila S, French JK, Thomas L: Left atrial volume and adverse cardiovascular outcomes in unselected patients with and without CKD. *Clin J Am Soc Nephrol* 9: 1369–1376, 2014
  16. Chan MY, Wong HB, Ong HY, Yeo TC: Prognostic value of left atrial size in chronic kidney disease. *Eur J Echocardiogr* 9: 736–740, 2008
  17. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Cataliotti A, Seminara G, Stancanelli B, Malatino LS: Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* 15: 1029–1037, 2004
  18. Sharma R, Pellerin D, Gaze DC, Mehta RL, Gregson H, Streather CP, Collinson PO, Brecker SJ: Mitral peak Doppler E-wave to peak mitral annulus velocity ratio is an accurate estimate of left ventricular filling pressure and predicts mortality in end-stage renal disease. *J Am Soc Echocardiogr* 19: 266–273, 2006
  19. Chen SC, Chang JM, Tsai YC, Huang JC, Chen LI, Su HM, Hwang SJ, Chen HC: Ratio of transmitral E-wave velocity to early diastole mitral annulus velocity with cardiovascular and renal outcomes in chronic kidney disease. *Nephron Clin Pract* 123: 52–60, 2013
  20. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39[Suppl 1]: S1–S266, 2002
  21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography: Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440–1463, 2005
  22. Wolkewitz M: Avoidable statistical pitfalls in analyzing length of stay in intensive care units or hospitals. *Crit Care* 18: 408, 2014
  23. Allignol A, Beyersmann J, Schmoor C: Statistical issues in the analysis of adverse events in time-to-event data. *Pharm Stat* 15: 297–305, 2016
  24. Deslandes E, Chevret S: Joint modeling of multivariate longitudinal data and the dropout process in a competing risk setting: Application to ICU data. *BMC Med Res Methodol* 10: 69, 2010
  25. Hatano S: Experience from a multicentre stroke register: A preliminary report. *Bull World Health Organ* 54: 541–553, 1976
  26. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; ESC Committee for Practice Guidelines (CPG): Third universal definition of myocardial infarction. *Eur Heart J* 33: 2551–2567, 2012
  27. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, Tritto I, Zannad F, Girerd N: Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail* 17: 1172–1181, 2015
  28. Huttin O, Marie PY, Benichou M, Bozec E, Lemoine S, Mandry D, Juillière Y, Sadoul N, Micard E, Duarte K, Beaumont M, Rossignol P, Girerd N, Selton-Suty C: Temporal deformation pattern in acute and late phases of ST-elevation myocardial infarction: Incremental value of longitudinal post-systolic strain to assess myocardial viability [published online ahead of print April 23, 2016]. *Clin Res Cardiol*
  29. Uno H, Tian L, Cai T, Kohane IS, Wei LJ: A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med* 32: 2430–2442, 2013
  30. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ: B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: Relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 46: 610–620, 2005
  31. Stewart GA, Foster J, Cowan M, Rooney E, McDonagh T, Dargie HJ, Rodger RS, Jardine AG: Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int* 56: 2248–2253, 1999
  32. Gruszczynska K, Krzych LJ, Gołba KS, Biernat J, Roleder T, Deja MA, Ulbrych P, Malinowski M, Janusiewicz P, Woś S, Baron J: Statistical agreement of left ventricle measurements using cardiac magnetic resonance and 2D echocardiography in ischemic heart failure. *Med Sci Monit* 18: MT19–MT25, 2012
  33. Troughton R, Michael Felker G, Januzzi JL Jr: Natriuretic peptide-guided heart failure management. *Eur Heart J* 35: 16–24, 2014
  34. Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, Zamorano J, Nihoyannopoulos P; European Association of Echocardiography: European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *Eur J Echocardiogr* 9: 438–448, 2008
  35. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM: Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 355: 1126–1130, 2000
  36. Berger R, Moertl D, Peter S, Ahmadi R, Huelsmann M, Yamuti S, Wagner B, Pacher R: N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure: a 3-arm, prospective, randomized pilot study. *J Am Coll Cardiol* 55: 645–653, 2010
  37. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Birmingham M, Patle A, Badabhagn MR, Murtagh G, Voon V, Tilson L, Barry M, McDonald L, Maurer B, McDonald K: Natriuretic peptide-based screening and collaborative care for heart failure: The STOP-HF randomized trial. *JAMA* 310: 66–74, 2013
  38. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, Leosco D, Perrone-Filardi P: Natriuretic peptide-guided therapy in chronic heart failure: A meta-analysis of 2,686 patients in 12 randomized trials. *PLoS One* 8: e58287, 2013

39. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL: 2013 ACCF/AHA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 128: 1810–1852, 2013
40. Felker GM, Ahmad T, Anstrom KJ, Adams KF, Cooper LS, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Leifer ES, Mark DB, Desvigne-Nickens P, Paynter G, Piña IL, Whellan DJ, O'Connor CM: Rationale and design of the

GUIDE-IT study: Guiding evidence based therapy using biomarker intensified treatment in heart failure. *JACC Heart Fail* 2: 457–465, 2014

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