Received: 13 June 2020 | Revised: 5 August 2020 | Accepted: 9 August 2020

DOI: 10.1111/nep.13776

ORIGINAL ARTICLE

NEPHROLOGY WILEY

N-acetyl-b-D-glucosaminidase: A potential cardiorenal biomarker with a relevant impact on ICD shock therapies and mortality

Raphael Allgaier[1] | Christina Strack[1] | Stefan Wallner[2] | Ute Hubauer[1] | Ekrem Uecer[1] | Petra Lehn[2] | Andreas Keyser[3] | Andreas Luchner[4] | Lars Maier[1] | Carsten Jungbauer[1]

[1]Department of Internal Medicine II, University Medical Center Regensburg, Regensburg, Germany

[2]Department of Clinical Chemistry and Laboratory Medicine, University Medical Center Regensburg, Regensburg, Germany

[3]Department of Cardiothoracic Surgery, University Medical Center Regensburg, Regensburg, Germany

[4]Department of Cardiology, Hospital Barmherzige Brüder Regensburg, Regensburg, Germany

Correspondence
Mr. Raphael Allgaier, Department of Internal Medicine II, University Medical Center Regensburg, Regensburg, Germany.
Email: raphael.allgaier@stud.uni-regensburg.de

Abstract

Aims: Chronic heart failure may lead to chronic kidney disease. Previous studies suggest tubular markers N-acetyl-b-D-glucosaminidase (NAG) and Kidney-injury-molecule-1 (KIM-1) as potential markers for the cardiorenal syndrome (CRS). The prognostic value of NAG and KIM-1 regarding implantable cardioverter defibrillator (ICD) shock therapies is unknown.

Methods: We included 314 patients with an ICD and collected plasma and urine samples. Urine-values of NAG and KIM-1 got related to urinary creatinine. Outcomes of interest were sustained adequate shock therapies and a combined endpoint of all-cause mortality, rehospitalisation due to congestive heart failure and adequate shock therapies. Follow up time was 32 months (IQR 6-35 months).

Results: KIM-1 and NAG were positively correlated with NT-proBNP (KIM-1: r = .34, P < .001; NAG: r = .47, P < .001). NAG was significantly elevated in patients with primary prevention compared with secondary prevention ICD indication (P = .003). According to Kaplan Meier analysis, NAG as well as NT-proBNP were significant predictors for adequate ICD shock therapies and for the combined endpoint (each P < .001). Elevated KIM-1 showed no significant differences (each P = n.s.). In multivariate cox regression analysis, NAG as well as NT-proBNP were both independent predictors for adequate ICD shock therapies as well as the combined endpoint, beside ejection fraction <35% (each P < .05). Diabetes, primary prevention ICD indication, coronary artery disease, eGFR and age were no significant predictors for both endpoints (each P = n.s.).

Conclusion: Similar to NT-proBNP, NAG showed promising value for overall prognostication in ICD patients. Especially, NAG seems to incorporate an additional prognostic value regarding occurrence of ICD shock therapies.

KEYWORDS

cardiorenal syndrome, ICD shock therapies, tubular markers

Chronic heart failure (CHF) is one of the main causes of death and presents a global public health problem.[1] Ventricular arrhythmias with consecutive Sudden Cardiac Death are potential outcomes of CHF and present a major cause for mortality.[1-3] For diagnosis of CHF, plasma NT-proBNP represents the gold standard.[4] Further, chronic kidney disease is often concomitant in CHF. The coexistence of cardial and renal dysfunction is described as cardiorenal syndrome (CRS).[5] In regard to diagnosis of CRS, tubular markers were studied to detect renal impairment in heart failure.[6-8] Originally, urinary KIM-1[9] and urinary NAG[10] as markers of tubular damage were investigated in acute kidney injury[11] then with reference to diagnosis and clinical outcome of CRS type 2, which describes chronic renal impairment based on CHF.[12] So far, KIM-1 and NAG were investigated mainly for prognostication of all-cause mortality and rehospitalisation due to congestive heart failure.[7,13]

However, it is unknown whether tubular markers can also predict clinical outcome regarding occurrence of ventricular arrhythmias. Prognostication of ventricular arrhythmias and Sudden Cardiac Death is a challenge so far. To identify high-risk patients, new biomarkers are required.[3] This is important, as especially high-risk patients may benefit from primary preventive implantable cardioverter defibrillator (ICD) implantation.[14] Further, ICD patients suffering from proceeding or advanced CRS may profit from a closer and more frequent surveillance. Aim of the current study was to assess if NAG, KIM-1 as well as NT-proBNP provide additional value regarding prognosis of ventricular arrhythmias and Sudden Cardiac Death. Therefore, we analysed a large cohort of ICD patients regarding occurrence of adequate ICD shock therapies.

SUMMARY AT A GLANCE

Among 314 patients with ICD, NAG levels were significantly associated with clinically important outcomes including sustained adequate shock therapies and a combined endpoint of all-cause mortality or rehospitalization. These findings suggest a possible link between kidney tubular injury and ventricular arrhythmias.

1 | METHODS

1.1 | Study population

Between October 2015 and April 2016 and between April 2018 and October 2018, a total of 314 patients with an ICD implanted at the university hospital of Regensburg were included in the study. Included were all patients with an ICD above 18 years who were treated in our out-patient clinic and who were able to sign the consent form. Exclusion criteria were severe chronic kidney disease (KDIGO eGFR category 5),[15] patients receiving hospital treatment due to acute cardiac or acute renal deterioration as well as all patients with CRT-P aggregates. Patients were included independent of primary or secondary prevention ICD indication. Indication for ICD implantation was according to specific ESC guidelines. Primary preventive ICD implantation was indicated in patients with severely reduced left ventricular ejection fraction and a failed trial of optimal medical therapy to increase the left ventricular ejection fraction to >35% accompanied by increased risk of Sudden Cardiac Death.[16] Secondary preventive ICD implantation was indicated in patients with documented ventricular fibrillation, haemodynamically not tolerated ventricular tachycardia or reanimated Sudden Cardiac Death due to malignant ventricular arrhythmias in the absence of reversible causes.[2] CKD was defined analogous to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as kidney damage (structural or functional abnormalities of the kidneys) for longer than 3 months, with or without decreased eGFR, or as declined kidney function with eGFR <60 mL/min per 1.73 m^2 for longer than 3 months, with or without structural or functional abnormalities of the kidneys.[15] In order to define CKD regarding KDIGO guidelines previous values of serum creatinine and eGFR were obtained from all patients.

Each patient was interviewed (New York Heart Association [NYHA] stage, drug therapy, pre-existing illnesses) and physically examined (weight, oedema, pulmonary rates, elevated jugular venous pressure). Ejection fraction (EF) was evaluated by echocardiography according to Simpsons's method. Estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI formula.[17]

As endpoints were used occurrence of adequate ICD shock therapies as well as a combined endpoint of all-cause mortality and rehospitalisation due to congestive heart failure as well as adequate ICD shock therapies. Ventricular arrhythmias receiving antitachycardia pacing therapies without shock therapy were not included. A follow up was performed up to April 2019, by telephone interviews and evaluation of hospital medical files, especially analysis of reports of ICD interrogations. Date of death was confirmed by hospital or death registries or by relatives.

The institutional ethics committee permitted an execution of this study. It was performed in agreement with good clinical practice guidelines and with the standards established for human experimentation by the Declaration of Helsinki.

2 | SAMPLE COLLECTION AND BIOCHEMICAL ANALYSES

At enrolment, blood and urine samples were collected on the same day. All patients were scheduled in the morning. Venepuncture was performed immediately after patient arrival in our outpatient clinic. Urine samples were collected by each patient from first-morning spot urine into prepared and in advance to the patient mailed sterile cups. Blood and urine samples were immediately sent to the central laboratory and NT-proBNP, serum as well as urinary creatinine (enzymatic) were immediately analysed on a Dimension Vista 1500 auto analyser (Siemens Healthineers). Serum creatinine was measured by enzymatic methods and Siemens test "ECREA." For analysis of the tubular

markers KIM-1 and NAG urine samples were aliquoted into 2 mL tubes and stored at −80°C. They were thawed directly before analysis. KIM-1 was measured with the KIM-1 ELISA Duo kit and the respective ancillary reagent kit (#DY1750B and #DY008, R&D Systems) according to the manufacturer's instructions. The NAG assay was performed with a modified protocol in 96 well plates (#10875406001, Roche Diagnostics). In brief 100 µL of substrate solution were used per well and pre-incubated for 5 minutes at 37°C. Then, 5 µL of sample, control or standard was added to the plate and shaken for 30 seconds. After an incubation for 60 minutes at 37°C, the reaction was stopped by the addition of 200 µL of stop solution followed by a final incubation for 10 minutes at 37°C. Absorbance was read at 580 nm. The standard curve was determined with undiluted, 1:2, 1:5, 1:7.5 and 1:10 diluted Roche standard solution. KIM-1 and NAG were normalized to urinary creatinine to compensate the influence of variable urinary concentration on concentration of urinary biomarkers. Normalization to urinary creatinine is the standard method used for spot urine parameters in clinical trials.[18]

3 | STATISTICS

Descriptive data are presented as mean (±SD) for normally distributed data or medians and IQR for non-normally distributed data. Correlation coefficients were estimated according to Spearman. Normally distributed values were evaluated with Student's unpaired two-sided *t*-test. Non-normally distributed variables were evaluated with the Mann-Whitney-*U* test. Boxplots were performed to analyse and visualize the differences in marker concentrations between patients with coronary artery disease and dilatative cardiomyopathy as well as channelopathy. The receiver operating curves (ROC) were calculated and the area under the curves (AUC) and 95% confidence intervals were estimated. For a follow-up analysis, we constructed Kaplan Meier survival curves reflecting the relationship between the probability of reaching the endpoints and time of follow-up. Median values were used as the binary cutpoints for KIM-1 (877.63 ng/g crea), NAG (2.43 U/g crea) and NT-proBNP (800.00 pg/mL). Mean follow-up time was 32 months (IQR 6-35 months). Multivariate cox proportional

TABLE 1 Baseline characteristics

	All (n = 314)	NAG < median (n = 157)	NAG ≥ median (n = 157)	*P*-values
Age (years)	61.7 (±14.8)	58.1 (±15.8)	65.4 (±12.9)	<.001
Male	265 (84.4%)	135 (86.0%)	130 (82.8%)	.44
Body mass index (kg/m^2)	28.69 (±5.64)	28.3 (±5.0)	29.1 (±6.2)	.61
Primary prevention ICD indication	143 (45.5%)	59 (37.6%)	84 (53.5%)	<.01
CRT-D	73 (23.2%)	31 (19.7%)	42 (26.8%)	.15
Coronary artery disease	142 (45.2%)	67 (42.7%)	75 (47.8%)	.14
DCM	76 (24.2%)	32 (20.4%)	44 (28.0%)	.11
Others[a]	96 (30.6%)	58 (36.8%)	38 (24.2%)	.04
Hypertension	191 (60.8%)	85 (54.1%)	106 (67.5%)	.02
Diabetes	72 (22.9%)	23 (14.6%)	49 (31.2%)	<.001
EF (%)	44 (IQR 34-55)	50 (IQR 38-58)	40 (IQR 31-50)	<.001
<35%	86 (27.4%)	32 (20.4%)	54 (34.3%)	<.01
CKD	128 (40.7%)	41 (26.1%)	87 (55.4%)	<.001
eGFR (mL/min per 1,73m^2)				
≥60	201 (64.0%)	119 (75.8%)	82 (52.2%)	<.001
45-59	51 (16.2%)	19 (12.1%)	32 (20.4%)	.07
30-44	50 (15.9%)	17 (10.8%)	33 (21.0%)	.01
15-29	12 (3.8%)	2 (1.3%)	10 (6.4%)	.02
Drug therapy				
ACE-I/ARB/ARNI	245 (83.4%)	116 (73.9%)	129 (82.2%)	.08
Aldosteron-Antagonist	165 (52.5%)	76 (48.4%)	89 (56.7%)	.14
Beta-Blocker	282 (89.8%)	133 (84.7%)	149 (94.9%)	<.01
Digitalis	34 (10.8%)	8 (53.3%)	26 (16.6%)	<.01
Calcium channel blocker	28 (8.9%)	13 (8.3%)	15 (9.5%)	.70
Diuretic	207 (65.9%)	84 (53.5%)	123 (78.3%)	<.001
KIM-1 (ng/g crea)	877.63 (IQR 555.98-1309.82)	694.69 (IQR 464.87-991.74)	1095.40 (IQR 730.22-1683.82)	<.001
NAG (U/g crea)	2.43 (IQR 1.48-3.94)			
NT-proBNP (pg/mL)	800.00 (IQR 263.00-2170.75)	402.00 (IQR 158.00-1094.50)	1345.00 (IQR 554.00-3125.50)	<.001

[a]others: secondary cardiomyopathy: 29 (9.2%), primary VF: 22 (7.0%), H(O)CM: 20 (6.4%), Brugada: 7 (2.2%), long-QT: 6 (1.9%), ARVD: 5 (1.6%), congenital heart defect: 2 (0.6%), TakoTsubo: 2 (0.6%), Non-compaction cardiomyopathy: 1 (0.3%), muscular dystrophy: 1 (0.3%), short-QT: 1 (0.3%).

TABLE 2 Marker concentrations according to heart failure severity, prevention and CKD

	NT-proBNP (pg/mL)	NAG (U/g crea)	KIM-1 (ng/g crea)		NT-proBNP (pg/mL)	NAG (U/g crea)	KIM-1 (ng/g crea)
EF ≥ 35%	530 IQR 170-1210	2.18 IQR 1.41-3.55	820 IQR 510-1260	EF < 35%	2200 IQR 1060-4970	3.13 IQR 1.95-5.46	1040 IQR 690-1430
NYHA ≥ 3	1220 IQR 530-3180	2.81 IQR 2.10-5.96	1060 IQR 670-1340	NYHA < 3	750 IQR 220-2020	2.26 IQR 1.47-3.87	870 IQR 530-1310
1° prevention	1080 IQR 360-2820	2.99 IQR 1.70-4.47	910 IQR 610-1370	2° prevention	630 IQR 190-1610	2.14 IQR 1.38-3.49	860 IQR 520-1290
CKD	1690 IQR 780-3800	3.40 IQR 2.20-5.64	990 IQR 650-1380	No CKD	420 IQR 150-1090	1.94 IQR 1.33-3.06	820 IQR 510-1250

hazard analysis was performed as stepwise regressions with backward elimination to evaluate prognostic value of each marker regarding the endpoints. Hereby we analysed NAG as well as NT-proBNP in cox regression model with clinically relevant covariates for both endpoints (eGFR, severely reduced EF, age, diabetes, coronary artery disease, primary prevention ICD indication). Commercially available statistical software packages were used for analysis (IBM SPSS statistics 25, SPSS INC., Chicago, Illinois; MedCalc 19.4.1, MedCalc Software Ltd, Ostend, Belgium).

4 | RESULTS

4.1 | Study population

Baseline characteristics are presented in Table 1. Mean age was 62 years and the majority of patients were men. About half of the patients had a secondary prevention indication for ICD implantation. Coronary artery disease was present in about half of the patients and DCM in about a quarter of the patients. Less than half of the patients were suffering from CKD. Severely reduced left ventricular function (EF <35%) was present in less than one-third of the patients.

4.2 | Tubular biomarkers in ICD patients

KIM-1 and NAG were significantly negatively correlated with Crea eGFR ($r = -.16$ as well as $r = -.37$, each $P < .001$), CystatinC eGFR ($r = -.27$ as well as $r = -.50$, each $P < .001$) and EF ($r = -.17$ as well as $r = -.30$, each $P < .001$).

KIM-1 and NAG were significantly positively correlated with NT-proBNP ($r = .34$ as well as $r = .47$, each $P < .001$) and NYHA stage ($r = .27$ as well as $r = .28$, each $P < .001$).

Each Marker was correlated with CKD stage (NT-proBNP: $r = .482$, $P < .001$; NAG: $r = .347$, $P < .001$; KIM-1: $r = .11$, $P = .04$). About one third of patients had an eGFR lower than 60 mL/min per 1.73m^2. eGFR lower than 30 mL/min per 1.73m^2 was present in 12 patients. Marker levels were significantly elevated in patients with initial CKD (each $P < .02$, Table 2). There were no relevant associations of KIM-1 and NAG levels according to CKD stages (Figure 1). Patients with primary prevention ICD indication showed higher concentrations of NAG ($P = .003$) and NT-proBNP ($P = .001$, Table 2) than patients with secondary prevention ICD indication, opposite to KIM-1 (P = n.s.). KIM-1, NAG and NT-proBNP were significantly elevated in severely symptomatic patients defined by NHYA stage ≥3 as well as in patients with reduced ejection fraction <35% (each $P < .05$, Table 2). Further, KIM-1, NAG and NT-proBNP were significantly elevated in patients suffering from ICM as well as DCM compared with Channelopathy (each $P < .01$, Figure 2). No marker showed significant differences between ICM and DCM (each P = n.s.).

NAG, KIM-1 as well as NT-proBNP were significantly elevated in deceased patients (each $P < .001$). NAG as well as NT-proBNP were significantly increased in patients with sustained adequate shock therapies during follow up (each $P < .05$), but not KIM-1 (P = n.s.). There was no association between marker levels and occurrence of ICD therapies by antitachycardia pacing without shock (each P = n.s.).

4.3 | Prognostication for shock therapy and combined endpoint

The average follow-up period was 32 months (IQR 6-35 months). During follow-up 37 (11.7%) patients died, 27 (8,6%) patients suffered from adequate shock therapies and 34 (10.8%) patients were rehospitalized due to congestive heart failure. Overall, 72 (22.9%) patients reached the combined endpoint.

Regarding adequate shock therapy, ROC analysis for NT-proBNP showed a higher AUC (0.70) than NAG (AUC: 0.64, Figure 3), but there was no significant difference evident between AUCs of both markers (P = n.s.). Regarding mortality, similar results could be obtained with also no significant difference between AUCs of NT-proBNP and NAG (NT-proBNP; AUC: 0.79 vs NAG; AUC: 0.70; P = n.s.; Figure 3).

According to Kaplan Meier analysis, patients with NAG ≥ median (2.43 U/g crea) had a higher rate of adequate shock therapies than patients with NAG < median (20/157 (12.7%) vs 7/157 (4.5%); $P = .006$, Figure 4). Higher NT-proBNP-levels (≥800.00 pg/mL) were associated with a higher rate of adequate shock therapies (19/157

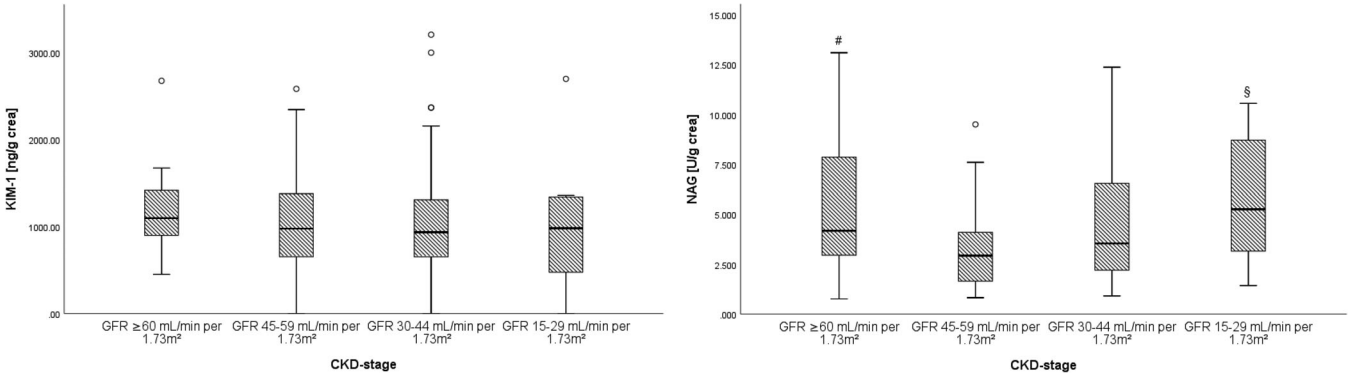

FIGURE 1 Boxplots: Marker levels of KIM-1 and NAG according to CKD stage (#: $P = .023$ vs eGFR 45-59 mL/min per 1.73m^2, §: $P = .013$ vs eGFR 45-59 mL/min per 1.73^2, all others: each P = n.s.)

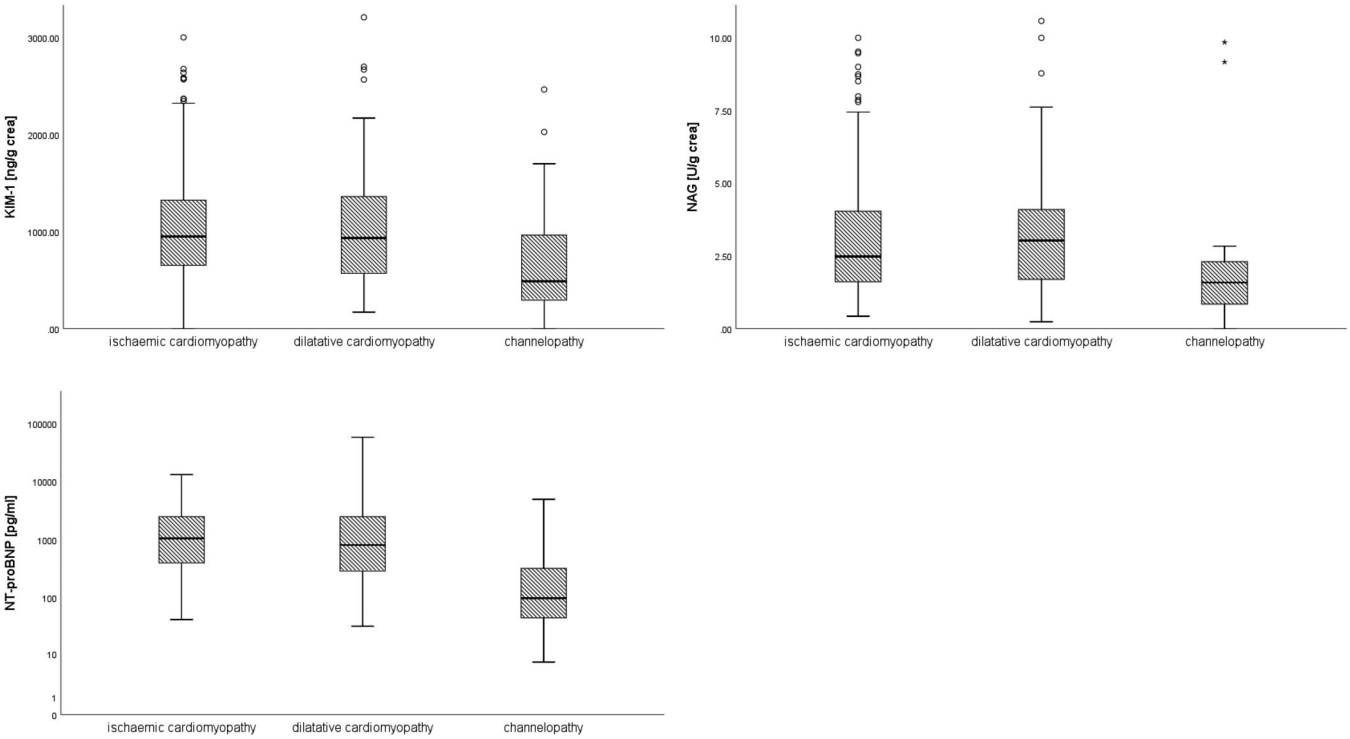

FIGURE 2 Boxplots: Marker levels of NT-proBNP, KIM-1 and NAG in patients suffering from ICM vs DCM vs Channelopathy

(12.1%) vs 8/157 (5.1%); P = .036, Figure 4). KIM-1 ≥ median (877.63 ng/g crea) was not associated with a higher rate of adequate shock therapies according to Kaplan Meier analysis (P = n.s.).

NAG ≥ median as well as NT-proBNP ≥ median were significant predictors for the combined endpoint (NAG: 51/157 (32.5%) vs 21/157 (13.3%); $P < .001$; NT-proBNP: 58/157 (36.9%) vs 14/157 (8.9%); $P < .001$, Figure 5), opposite to KIM-1 ≥ median (P = n.s.).

According to Cox regression analysis, NAG as well as NT-proBNP were both independent predictors for adequate shock therapy as well as the combined endpoint, beside severely reduced ejection fraction (each $P < .05$, Tables 3 and 4). Diabetes, primary prevention ICD indication, coronary artery disease, age and eGFR were no significant predictors for both endpoints (each P = n.s.).

5 | DISCUSSION

In the current study, we evaluated the tubular markers NAG and KIM-1 regarding their capacity to predict occurrence of ventricular arrhythmias and adequate ICD shock therapies. Therefore, tubular markers as well as NT-proBNP as an established marker for heart failure were investigated in a mixed cohort of patients with ICD. Especially NAG showed prognostic capabilities regarding occurrence of adequate shock therapies similar to NT-proBNP. For antitachycardia pacing without shock therapy no association with a marker could be shown. NAG and NT-proBNP seem to incorporate predictive value regarding fast ventricular tachycardias and ventricular fibrillation, but not regarding monomorphic slow ventricular tachycardias.

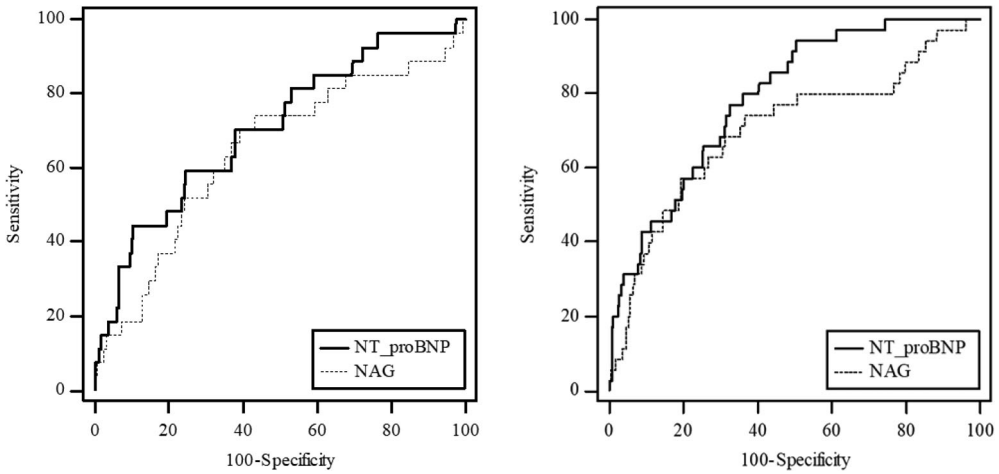

FIGURE 3 Left: Receiver operating characteristic analysis for shock therapy in the overall cohort; area under the curves (AUC) of NT-proBNP and NAG in regard to occurrence of shock therapy. NT-proBNP; AUC: 0.70 vs NAG; AUC: 0.64, *P* = n.s.. Right: Receiver operating characteristic analysis for mortality in the overall cohort; area under the curves (AUC) of NT-proBNP and NAG in regard to occurrence of mortality. NT-proBNP; AUC: 0.79 vs NAG; AUC: 0.70, *P* = n.s.

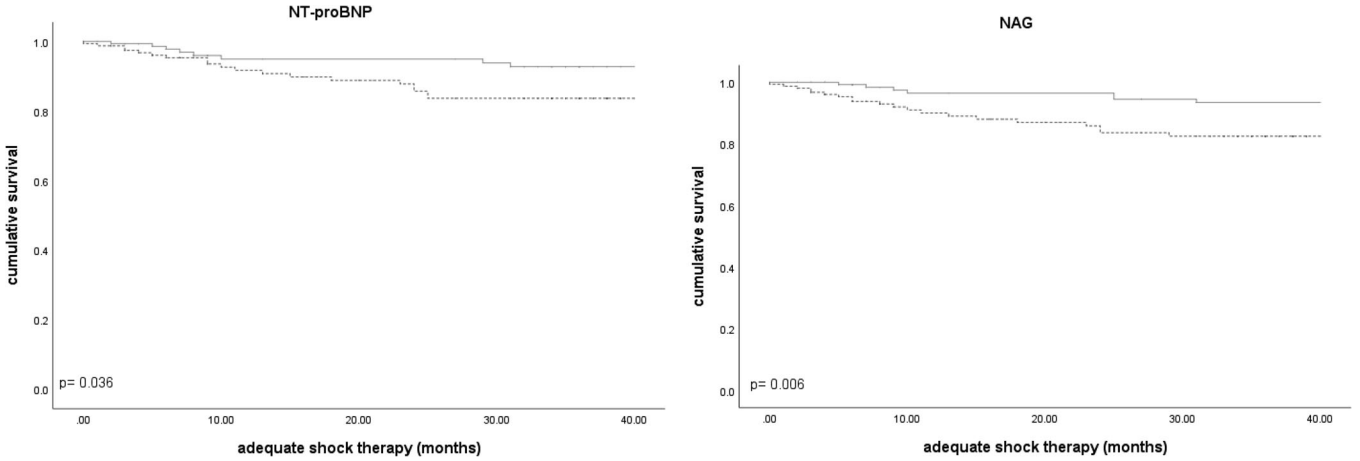

FIGURE 4 NT-proBNP and NAG: Kaplan Meier curves regarding shock therapy. Left: ·····, NT-proBNP ≥800.00 pg/mL; —— NT-proBNP <800.00 pg/mL; Right: ·····, NAG ≥2.43 U/g crea; —— NAG <2.43 U/g crea

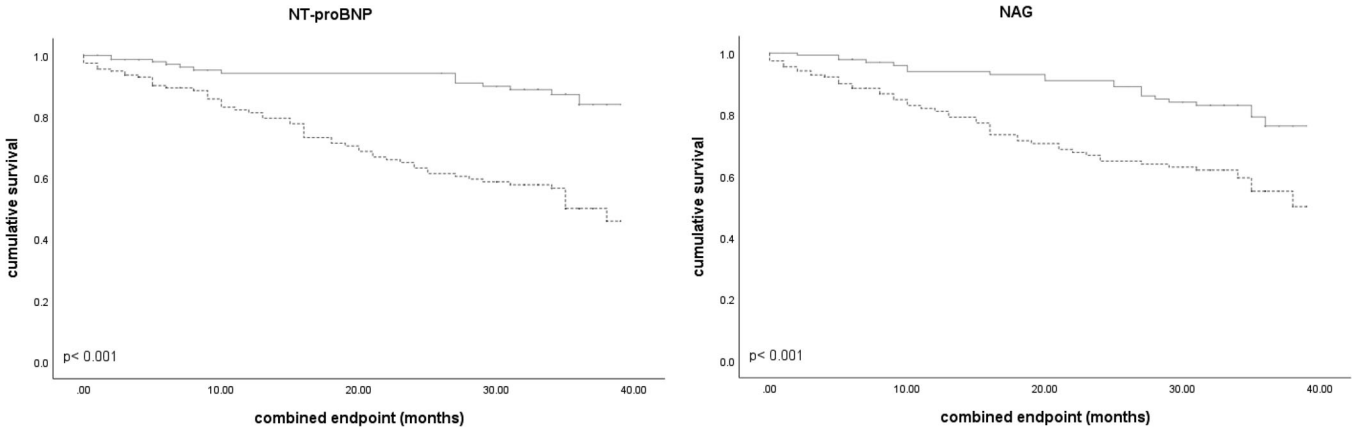

FIGURE 5 NT-proBNP and NAG: Kaplan Meier curves regarding the combined endpoint. Left: ·····, NT-proBNP ≥800.00 pg/mL; —— NT-proBNP <800.00 pg/mL; Right: ·····, NAG ≥2.43 U/g crea; —— NAG <2.43 U/g crea

Furthermore, NAG and NT-proBNP were independent predictors for a combined endpoint, composed of all-cause mortality, adequate shock therapies and rehospitalisation due to congestive heart failure. The prognostic power of NAG and NT-proBNP regarding detection of shock therapy as well as detection of mortality seem to be similar. No significant difference could be shown in ROC analysis. Nevertheless, there was a trend to higher AUCs regarding the established heart failure marker NT-proBNP. The association of NAG as a renal marker

TABLE 3 NAG and NT-proBNP: Cox regression analysis regarding shock therapy

Risk factors	NAG *P*-value	HR	95% CI	NT-proBNP/100 *P*-value	HR	95% CI
Marker	.01	1.058	1.013-1.105	<.01	1.005	1.002-1.009
Severely reduced EF (<35%)	.01	2.841	1.244-6.485	<.05	2.422	1.022-5.742
Coronary artery disease	.12	0.479	0.191-1.204	.15	0.506	0.201-1.275
Primary prevention ICD indication	.15	0.529	0.224-1.247	.18	0.555	0.234-1.316
Age	.34	0.984	0.952-1.017	.20	0.978	0.946-1.012
eGFR	.58	0.994	0.974-1.015	.48	0.992	0.971-1.014
Diabetes	.51	0.681	0.217-2.136	.56	0.713	0.226-2.250

TABLE 4 NAG and NT-proBNP: Cox regression analysis regarding the combined endpoint

Risk factors	NAG *P*-value	HR	95% CI	NT-proBNP/100 *P*-value	HR	95% CI
Marker	<.01	1.062	1.029-1.095	<.01	1.006	1.003-1.008
Severely reduced EF (<35%)	<.01	2.123	1.291-3.491	.02	1.867	1.118-3.120
Coronary artery disease	.57	1.157	0.697-1.921	.46	1.210	0.728-2.009
Primary prevention ICD indication	.51	1.183	0.721-1.939	.47	1.203	0.733-1.976
Age	.74	1.004	0.981-1.028	.90	0.998	0.975-1.022
eGFR	.08	0.989	0.976-1.001	.07	0.988	0.975-1.001
Diabetes	.13	0.638	0.355-1.144	.21	0.687	0.381-1.240

with cardiac arrhythmias provides new benefit and confirms the role of NAG as marker of cardiorenal syndrome. KIM-1 as well as kidney function estimated by eGFR correlated to NAG and NT-proBNP, but were not associated with adequate shock therapies in a mean follow-up time of 32 months.

5.1 | Prognostication of tubular and cardial markers

To our knowledge, the current study is the first one to evaluate candidate tubular biomarkers NAG and KIM-1 regarding their prognostic capacity for ventricular arrhythmias in patients with ICD. Therefore, our findings of NAG as an independent predictor for ventricular arrhythmias provide potentially an additional value regarding risk evaluation of ventricular arrhythmias in heart failure. Damman et al assessed in a large cohort the clinical outcome of CHF patients, measured by mortality and rehospitalisation and reported similar results. Opposite to the current study, they did not investigate adequate ICD shock therapies.[13]

In contrast to KIM-1, NAG could be shown as an independent predictor for our combined endpoint. In accordance to Jungbauer et al, NAG and KIM-1 were also shown as an independent predictor for a combined endpoint of all-cause mortality and rehospitalisation due to congestive heart failure (data not shown).[7] The mean follow-up time was about 52 months, while the current study had a mean follow-up time of 32 months and investigated also adequate ICD shock therapies.

Consistent with our findings of association between NT-proBNP and adequate shock therapies, Levine et al also reported increased levels of NT-proBNP as predictor for ventricular arrhythmias in a cohort of only primary prevention ICD indication[19] whereas Klein et al could not show an association between NT-proBNP and occurrence of ventricular arrhythmias.[20] The latter cohort included almost solely patients with secondary prevention ICD indication and the mean follow up time was about half as long as in the current study. Therefore, direct comparisons seem not to be feasible. Simsek et al could show associations between NT-proBNP and mortality.[21] In the current study, NT-proBNP is associated with the combined endpoint consisting of mortality, adequate shock therapies and rehospitalisation due to congestive heart failure. NT-proBNP is an established marker for heart failure, which is associated with mortality and hospitalization.[4,22] Thereby, our findings are conform. According to available data, NT-proBNP seems not only to be a marker for heart failure, but also to be relevant in risk stratification for ventricular arrhythmias. Decreasing systolic heart function, volume overload and sequentially myocardial stretching are the main trigger for secretion of NT-proBNP and a risk factor for increased vulnerability for arrhythmias.[23-25]

5.2 | Association between NAG and ventricular arrhythmias

Cardial and renal function are strongly dependent and coexistence of cardial and renal dysfunction is described as cardiorenal syndrome. Worsening of one causes worsening of the other.[26] Pathophysiological aspects are not fully understood. Hypoperfusion and neurohormonal abnormalities are predominantly discussed.[12] Tubular impairment leads to secretion of NAG and KIM-1 in the urine.[9,10] They can already be measured without decline of glomerular filtration

rate and with preserved renal function.[27] The capability of tubular markers NAG and KIM-1 to identify subclinical renal impairment in patients with CHF affirm their usefulness as cardiorenal markers.[6,8] Elevated values of NAG and KIM-1 are indicators of a proceeding CRS.[8] Worsening heart function accompanies higher risk for arrhythmogen events and mortality.[28,29] In the current study, NAG seemed to incorporate prognostic value regarding ventricular arrhythmias, opposite to KIM-1.

Accordingly, the current results confirm the transition from AKI diagnosis markers to markers of CRS.[8] Additionally, the results suggest to extend the prognostic value of tubular markers regarding risk stratification for arrhythmogen events in CHF. The potential usefulness of tubular markers to predict cardial outcome verifies the importance and dependence on renal function in patients with CHF. Worsening renal function may lead to electrolyte shifting and especially deviant potassium serum concentrations are associated with arrthymogen events.[30] To confirm this hypothesis, more investigations are necessary.

5.3 | Utilization in clinical practice

Potentially, NT-proBNP as well as NAG may contribute to identify patients with high-risk for ventricular arrhythmias and Sudden Cardiac Death. Patients with ICD and proceeding or advanced CRS measured by tubular markers may benefit from closer and more frequent surveillance. Periodical measurements of electrolytes, especially of potassium as well as targeted handling of antiarrhythmic drugs as well as optimized ICD adjustments may be useful in treatment of these patients. Potentially, reaching the endpoints (shock therapies, rehospitalisation, mortality) can be avoided or delayed by improved, well-timed and adapted treatment of CRS in high-risk patients. Moreover, NAG and NT-proBNP may contribute to differentiate patients, who will profit from ICD implantation. On the one hand, Sudden Cardiac Death is a major public health problem and preventive ICD-implantation can reduce mortality by Sudden Cardiac Death.[1,14] On the other hand, only few patients with ICD are receiving shock therapy, consistent with the current study.[31,32] However, the use of NAG in daily practice requires further investigation.

6 | LIMITATIONS

This was a single-centre study of 314 patients. Patients with terminal CKD were excluded and 84% were men. Therefore, severely ill patients and women may be underrepresented. Hereby, we could avoid accumulation of markers at patients without urinary elimination on dialysis. Further, only 27 patients reached the endpoint of adequate ICD shock therapy, but we should consider that only a small number of patients with ICD receive shocks at all. The detailed circumstances of ventricular arrhythmia and ICD shock therapy were not analysed, for example, electrolytes at the time of shock therapies were not evaluated. Ventricular arrhythmias at a frequency underneath the adjusted frequency for shock therapy were not considered. Nevertheless, further studies are necessary to characterize more precisely the relationship between tubular markers and the occurrence of ventricular arrhythmias.

The current study investigated the tubular markers NAG and KIM-1 as well as NT-proBNP as an established marker for heart failure in an ICD-cohort. Similar to NT-proBNP, NAG showed promising value for overall prognostication in ICD patients. Especially, NAG seems to incorporate an additional prognostic value regarding occurrence of adequate ICD shock therapies. Overall, this was the first study to our knowledge, which reported association between tubular markers and occurrence of ventricular arrhythmias. Therefore, further investigations are necessary to confirm these results.

DECLARATION OF INTEREST

None declared.

ORCID

Raphael Allgaier https://orcid.org/0000-0002-4845-447X

REFERENCES

1. Srinivasan NT, Schilling RJ. Sudden cardiac death and arrhythmias. *Arrhythmia Electrophysiol Rev*. 2018;7(2):111-117.
2. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the Management of Patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36(41):2793-2867.
3. Wellens HJJ, Schwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J*. 2014;35(25):1642-1651.
4. McKie PM, Burnett JC. NT-proBNP: the gold standard biomarker in heart failure. *J Am Coll Cardiol*. 2016;68(22):2437-2439.
5. Ronco C, House AA, Haapio M. Cardiorenal and renocardiac syndromes: the need for a comprehensive classification and consensus. *Nat Clin Pract Nephrol*. 2008;4(6):310-311.
6. Damman K, van Veldhuisen DJ, Navis G, et al. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. *Heart*. 2010;96(16):1297-1302.
7. Jungbauer CG, Birner C, Jung B, et al. Kidney injury molecule-1 and N-acetyl-β-D-glucosaminidase in chronic heart failure: possible biomarkers of cardiorenal syndrome. *Eur J Heart Fail*. 2011;13(10):1104-1110.
8. Jungbauer CG, Uecer E, Stadler S, et al. N-acteyl-ß-D-glucosaminidase and kidney injury molecule-1: new predictors for long-term progression of chronic kidney disease in patients with heart failure. *Nephrology (Carlton)*. 2016;21(6):490-498.
9. Ichimura T, Mou S. Kidney injury molecule-1 in acute kidney injury and renal repair: a review. *Zhong Xi Yi Jie He Xue Bao*. 2008;6(5):533-538.
10. Price RG. The role of NAG (N-acetyl-beta-D-glucosaminidase) in the diagnosis of kidney disease including the monitoring of nephrotoxicity. *Clin Nephrol*. 1992;38(Suppl 1):S14-S19.
11. Bonventre JV. Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. *Nephrol Dial Transplant*. 2009;24(11):3265-3268.
12. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527-1539.

13. Damman K, Masson S, Hillege HL, et al. Tubular damage and worsening renal function in chronic heart failure. *JACC Heart Fail*. 2013;1(5):417-424.
14. Kolodziejczak M, Andreotti F, Kowalewski M, et al. Implantable cardioverter-defibrillators for primary prevention in patients with ischemic or nonischemic cardiomyopathy: a systematic review and meta-analysis. *Ann Intern Med*. 2017;167(2):103-111.
15. Chapter 1: definition and classification of CKD. *Kidney Int Suppl (2011)*. 2013;3(1):19-62.
16. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
18. Brott DA, Adler SH, Arani R, Lovick SC, Pinches M, Furlong ST. Characterization of renal biomarkers for use in clinical trials: biomarker evaluation in healthy volunteers. *Drug Des Devel Ther*. 2014;8:227-237.
19. Levine YC, Rosenberg MA, Mittleman M, et al. B-type natriuretic peptide is a major predictor of ventricular tachyarrhythmias. *Heart Rhythm*. 2014;11(7):1109-1116.
20. Klein G, Lissel C, Fuchs A-C, et al. Predictors of VT/VF-occurrence in ICD patients: results from the PROFIT-study. *Europace*. 2006;8(8):618-624.
21. Simsek MA, Degertekin M, Turer Cabbar A, et al. NT-proBNP levels and mortality in a general population-based cohort from Turkey: a long-term follow-up study. *Biomark Med*. 2018;12(10):1073-1081.
22. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239.
23. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail*. 2004;6(3):257-260.
24. Lorvidhaya P, Addo K, Chodosh A, Iyer V, Lum J, Buxton AE. Sudden cardiac death risk stratification in patients with heart failure. *Heart Fail Clin*. 2011;7(2):157-174. vii.
25. Stehlik J, Feldman DS. Arrhythmias in heart failure: beyond sudden cardiac death. *Curr Opin Cardiol*. 2013;28(3):315-316.
26. Ronco C, Bellasi A, Di Lullo L. Cardiorenal syndrome: an overview. *Adv Chronic Kidney Dis*. 2018;25(5):382-390.
27. Damman K, Masson S, Hillege HL, et al. Clinical outcome of renal tubular damage in chronic heart failure. *Eur Heart J*. 2011;32(21):2705-2712.
28. Vest RN, Gold MR. Risk stratification of ventricular arrhythmias in patients with systolic heart failure. *Curr Opin Cardiol*. 2010;25(3):268-275.
29. Beaser AD, Cifu AS, Nayak HM. Primary prevention of sudden cardiac death. *JAMA*. 2019;322(2):161-162.
30. Podrid PJ. Potassium and ventricular arrhythmias. *Am J Cardiol*. 1990;65(10):33E-44E. discussion 52E.
31. Klein L, Hsia H. Sudden cardiac death in heart failure. *Cardiol Clin*. 2014;32(1):135-144. ix.
32. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375(13):1221-1230.

How to cite this article: Allgaier R, Strack C, Wallner S, et al. N-acetyl-b-D-glucosaminidase: A potential cardiorenal biomarker with a relevant impact on ICD shock therapies and mortality. *Nephrology*. 2020;25:888–896. https://doi.org/10.1111/nep.13776