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ORIGINAL RESEARCH

HEART FAILURE

Natriuretic Peptides, Kidney Function, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND N-terminal pro-B-type natriuretic peptides (NT-proBNPs) are guideline-recommended biomarkers for risk stratification in patients with heart failure. However, NT-proBNP levels are often elevated in chronic kidney disease, introducing uncertainty about their prognostic relevance in persons across a broad range of estimated glomerular filtration rate (eGFR).

OBJECTIVES The aim of this study was to assess the association of NT-proBNP with cardiovascular and mortality outcomes in patients with heart failure and mildly reduced or preserved ejection fraction, stratified by baseline kidney function.

METHODS A pooled analysis was conducted of participants with NT-proBNP and eGFR measured at baseline in the I-PRESERVE (Irbesartan in Heart Failure and Preserved Ejection Fraction), TOPCAT (Americas region) (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function), PARAGON (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction), and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trials. The relationship between NT-proBNP and eGFR was assessed using piecewise linear regression. Using multivariable Cox and Poisson regression models, the association of NT-proBNP with outcomes across a range of eGFR was evaluated. The primary outcome was hospitalization for heart failure or cardiovascular death.

RESULTS Among 14,831 participants (mean age: 72.1 years; 50.3% female; mean eGFR: 63.3 mL/min/1.73 m^2, and median NT-proBNP: 840 pg/mL) followed up for a median 33.5 months, there were 3,092 primary outcomes. NT-proBNP levels increased by 9%, 8%, and 23% per 10 mL/min/1.73 m^2 lower eGFR in patients with baseline eGFR ≥60, 45-<60, and <45 mL/min/1.73 m^2, respectively (P for nonlinearity < 0.001). Each doubling in NT-proBNP was associated with a 37% relative increase in the primary outcome (HR: 1.37; 95% CI: 1.34-1.41), consistent across different eGFR categories (P for interaction = 0.42). For the same incidence of the primary outcome, NT-proBNP levels were approximately 2.5- to 3.5-fold lower in patients with eGFR <45 mL/min/1.73 m^2, compared with patients with eGFR ≥60 mL/min/1.73 m^2. Similar patterns were observed across all outcomes studied, including cardiovascular and noncardiovascular death.

CONCLUSIONS The same NT-proBNP concentration predicts a substantially higher absolute risk of adverse outcomes for people with heart failure and reduced kidney function, compared with those with preserved kidney function. These data call into question proposals for higher NT-proBNP references ranges in people with CKD, and suggest that reduced kidney function per se should not be a reason to disregard higher NT-proBNP levels. (JACC Heart Fail. 2025;13:28-39) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Chronic kidney disease (CKD) is one of the most frequently encountered comorbidities in patients with heart failure, affecting approximately 40% of individuals.[1] The presence of CKD in persons with heart failure is associated with an increased risk of disease progression, hospitalization, and mortality, the magnitude of which increases as kidney function decreases.[2] Thus, accurate assessment of risk may be important to guide clinical decision-making in this vulnerable population.

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are widely used in persons with heart failure, and their measurement is strongly guideline-recommended to diagnose, stratify risk, and monitor disease progression.[3] However, the presence of CKD complicates the interpretation of natriuretic peptides.

NT-proBNP concentrations are elevated in CKD; this may be related to either decreased clearance by the kidney, increased severity of heart disease, or both.[4,5] Consequently, there has been uncertainty about the prognostic relevance of NT-proBNP for heart failure outcomes in persons with different levels of kidney function. Indeed, the concentration of NT-proBNP that confers an equivalent absolute risk of heart failure hospitalization or cardiovascular death at different levels of kidney function is unknown.

We therefore conducted a pooled individual participant data analysis of 4 large-scale randomized trials of patients with heart failure with mildly reduced or preserved ejection fraction to better understand the prognostic relevance of NT-proBNP across different levels of kidney function for key cardiovascular and mortality outcomes.

METHODS

We used pooled individual participant data from 4 large-scale, randomized, double-blind, placebo-controlled outcome trials enrolling participants with heart failure with mildly reduced or preserved ejection fraction: I-PRESERVE (Irbesartan in Heart Failure and Preserved Ejection Fraction), TOPCAT-Americas (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function), PARAGON (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction), and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure). The design and primary results of these trials have been previously published.[6-9] In brief, I-PRESERVE, TOPCAT, and PARAGON all recruited participants with heart failure and left ventricular ejection fraction ≥45%, whereas DELIVER recruited those with heart failure and left ventricular ejection fraction >40%. Participants were randomized to irbesartan (I-PRESERVE), spironolactone (TOPCAT), dapagliflozin (DELIVER), or matching placebo. In the active-controlled PARAGON-HF trial, participants were randomized to sacubitril/valsartan or valsartan after a single-blind run-in phase in which participants were treated sequentially with half-target doses of both study drugs. In TOPCAT, analyses were restricted to participants recruited from the United States, Canada, Brazil, and Argentina (TOPCAT-Americas), given the significant regional heterogeneity observed.[10] Median follow-up ranged from 27.6 months in DELIVER to 49.5 months in I-PRESERVE. Trial protocols were approved by institutional ethics committees at all sites and all participants provided written informed consent.

Natriuretic peptides were incorporated variably into the inclusion criteria of each trial (Supplemental Table 1). NT-proBNP was part of the inclusion criteria for DELIVER (≥300-600 pg/mL) and PARAGON

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

NT-proBNP = N-terminal pro-B-type natriuretic peptide

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(≥200-900 pg/mL), with levels required for trial entry differing depending on history of heart failure hospitalization and atrial fibrillation. Participants in TOPCAT were enrolled based on hospitalization for heart failure within 12 months before randomization or an NT-proBNP ≥360 pg/mL (or BNP ≥100 pg/mL). NT-proBNP was not part of the inclusion criteria in I-PRESERVE.

The estimated glomerular filtration rate (eGFR) or serum creatinine inclusion criteria varied across trials. In DELIVER, the lower limit was an eGFR of ≥25 mL/min/1.73 m^2; in PARAGON-HF, participants were enrolled down to an eGFR of 30 mL/min/1.73 m^2 at screening or 25 mL/min/1.73 m^2 at randomization. In TOPCAT it was an eGFR ≥30 mL/min/1.73 m^2 or serum creatinine >221 mmol/L (2.5 mg/dL); in I-PRESERVE it was a serum creatinine >221 mmol/L (2.5 mg/dL).

eGFR AND NT-proBNP. The pooled population across the 4 trials was restricted to those with complete information on eGFR and NT-proBNP at baseline. Creatinine-based eGFR at baseline was recalculated using the CKD-Epidemiology Collaboration 2009 equation because this was reference standard during the time in which the trials were conducted. In I-PRESERVE, PARAGON-HF, and DELIVER, NT-proBNP was measured by a central trial laboratory using a sandwich immunoassay on an Elecsys platform (Roche Diagnostics).[11-13] In TOPCAT, NT-proBNP was measured at the local laboratory by each participating hospital.[14] Given the skewed distribution of NT-proBNP, all values were log-transformed before analysis.

OUTCOMES. The primary outcome in this analysis was hospitalization for heart failure or cardiovascular death. Other outcomes included: hospitalization for heart failure; cardiovascular death; noncardiovascular death; and all-cause mortality. All cardiovascular and mortality outcomes were independently adjudicated by blinded expert committees.

STATISTICAL ANALYSIS. Baseline characteristics of participants across different levels of eGFR (<45, 45 to <60, and ≥60 mL/min/1.73 m^2) were compared using chi-squared and ANOVA (analysis of variance) tests for categorical and continuous variables.

We evaluated the association between eGFR and NT-proBNP using multivariable linear regression with eGFR fitted using piecewise linear spline with knots at 45 and 60 mL/min/1.73 m^2, based on the Kidney Disease Improving Global Outcomes definition and classification of CKD. Models were adjusted for trial, treatment allocation, age, sex, race, history of diabetes, myocardial infarction, atrial fibrillation, body mass index (BMI), systolic blood pressure, left ventricular ejection fraction, and loop diuretic use at baseline. BMI and systolic blood pressure were fitted continuously using cubic splines with 3 knots. Because of the nonlinear relationship between eGFR and NT-proBNP, we assessed the association between eGFR and NT-proBNP in each eGFR category separately.

Association between NT-proBNP and clinical outcomes across different levels of kidney function were evaluated using multivariable Cox regression models adjusted for the covariates already listed. We log-transformed NT-proBNP using a base-2 logarithm with 500 pg/mL as the reference value to estimate HRs per doubling of NT-proBNP. To address potential competing risks of death, in sensitivity analysis, we constructed a separate competing risks regression model using the Fine and Gray method for the primary outcome, accounting for competing risk of noncardiovascular death, and for hospitalization for heart failure, accounting for competing risk of all-cause death.[15] The proportional hazards assumption was checked graphically using log-log plots.

To understand the equivalent absolute risk associated with a given NT-proBNP level in participants with different levels of kidney function, we calculated the incidence rate (per 100 patient-years) for any given NT-proBNP level (continuously and categorized as ≤500, >500 to ≤1,000, and >1,000 pg/mL) stratified by baseline eGFR (<45, 45 to <60, and ≥60 mL/min/1.73 m^2) using Poisson regression. We then compared the equivalent NT-proBNP concentration corresponding to an unadjusted event rate of 5 and 10 per 100 patient-years in patients with different levels of eGFR. We conducted subgroup analyses according to age, sex, diabetes status, BMI, and history of atrial fibrillation. In sensitivity analyses for the primary outcome, we standardized these estimates for the mean age, BMI, and proportion of participants with atrial fibrillation in the pooled cohort owing for the fact that these 3 variables differed across eGFR categories and are known to influence NT-proBNP levels.[16]

All analyses were conducted using Stata version 18.0.

RESULTS

We found that 14,831 participants across the 4 trials had complete data on NT-proBNP and eGFR. Mean age was 72.1 years, 50.3% were female, 24.5% had a history of myocardial infarction, and 40.1% had diabetes. The mean eGFR was 63.3 mL/min/1.73 m^2 and the median NT-proBNP was 840 pg/mL (25th-75th

TABLE 1 Baseline Characteristics of Participants According to eGFR at Baseline

	eGFR >60 mL/min/1.73 m² (n = 8,221)	eGFR 45-<60 mL/min/1.73 m² (n = 3,825)	eGFR <45 mL/min/1.73 m² (n = 2,785)	*P* Value
Trial				<0.001
DELIVER	3,192 (38.8)	1,657 (43.3)	1,412 (50.7)	
I-PRESERVE	2,312 (28.1)	714 (18.7)	429 (15.4)	
TOPCAT	163 (2.0)	120 (3.1)	76 (2.7)	
PARAGON	2,554 (31.1)	1,334 (34.9)	868 (31.2)	
Age, y	69.8 ± 8.4	74.1 ± 7.9	76.0 ± 8.1	<0.001
Male	4,292 (52.2)	1,863 (48.7)	1,222 (43.9)	<0.001
Race				0.13
White	6,616 (80.5)	3,039 (79.5)	2,175 (78.1)	
Black	193 (2.3)	93 (2.4)	79 (2.8)	
Asian	1,018 (12.4)	513 (13.4)	397 (14.3)	
Other	394 (4.8)	180 (4.7)	134 (4.8)	
Hypertension	7,368 (89.6)	3,497 (91.4)	2,612 (93.8)	<0.001
Diabetes mellitus	3,021 (36.7)	1,539 (40.2)	1,392 (50.0)	<0.001
Myocardial infarction	2,026 (24.6)	950 (24.8)	655 (23.5)	0.41
Stroke or TIA	710 (8.6)	414 (10.8)	344 (12.4)	<0.001
Atrial fibrillation	3,541 (43.1)	2,066 (54.0)	1,524 (54.7)	<0.001
Systolic BP, mm Hg	131.6 ± 15.3	130.1 ± 15.9	129.4 ± 16.2	<0.001
BMI, kg/m²	29.9 ± 5.5	30.0 ± 5.6	30.1 ± 5.9	0.09
eGFR, mL/min/1.73 m²	77.5 ± 12.0	52.2 ± 4.3	36.7 ± 5.4	<0.001
LVEF, %	56.5 ± 9.0	56.6 ± 8.6	56.7 ± 8.8	0.53
NT-proBNP, pg/mL	701 (357-1,279)	945 (501-1,714)	1,250 (631-2,312)	<0.001
NYHA functional class				<0.001
I	73 (0.9)	42 (1.1)	31 (1.1)	
II	5,094 (62.0)	2,498 (65.3)	1,742 (62.5)	
III	2,987 (36.3)	1,259 (32.9)	973 (34.9)	
IV	66 (0.8)	24 (0.6)	39 (1.4)	
ACEI or ARB	6,178 (75.2)	2,887 (75.5)	2,013 (72.3)	0.005
Beta-blocker	6,265 (76.3)	2,906 (76.0)	2,116 (76.0)	0.93
MRA	2,379 (29.5)	1,177 (31.8)	865 (31.9)	0.011
Loop diuretic	5,442 (66.2)	2,855 (74.7)	2,296 (82.4)	<0.001

Values are n (%), mean ± SD, or median (Q1-Q3), unless otherwise indicated.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; DELIVER = Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; eGFR = estimated glomerular filtration rate; I-PRESERVE = Irbesartan in Heart Failure and Preserved Ejection Fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PARAGON = Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction; TIA = transient ischemic attack; TOPCAT = Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function.

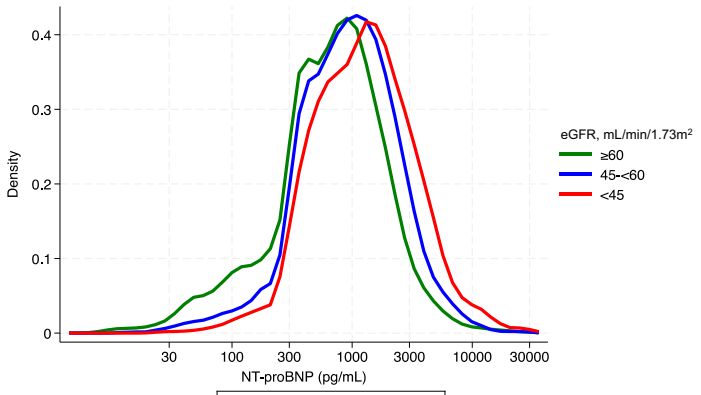
percentile: 424-1,566 pg/mL). Across progressively lower categories of eGFR, participants were more likely to be older, female, and have atrial fibrillation, diabetes, and hypertension (all $P < 0.0001$) (Table 1). They were also more likely to be receiving loop diuretic agents at baseline ($P < 0.001$) (Table 1).

Median NT-proBNP levels were higher across lower eGFR categories (Figure 1). The association between NT-proBNP and eGFR was nonlinear; each 10 mL/min/1.73 m² reduction in eGFR was associated with a 9%, 8%, and 23% higher NT-proBNP for participants with baseline eGFR ≥60, 45 to <60, and <45 mL/min/1.73 m², respectively (Figure 2). Distribution of NT-proBNP and eGFR values at an individual patient level are displayed in Supplemental Figure 1.

Over a median follow-up of 33.5 months, 3,092 participants were hospitalized for heart failure or died due to cardiovascular causes; 2,184 were hospitalized for heart failure; 1,465 died due to cardiovascular causes; 1,049 died due to noncardiovascular causes; 2,514 died due to any cause.

In fully adjusted models, each doubling in NT-proBNP was associated with a 37% relative increase in the primary outcome of hospitalization for heart failure or cardiovascular death (HR: 1.37; 95% CI: 1.34-1.41) (Figure 3). The relationship between NT-proBNP and the primary outcome was consistent across different levels of kidney function (P interaction = 0.42). Similar relationships were observed for other outcomes (Figure 3). Results were similar in sensitivity analyses for the primary

FIGURE 1 Distribution of NT-proBNP Across Different Levels of eGFR

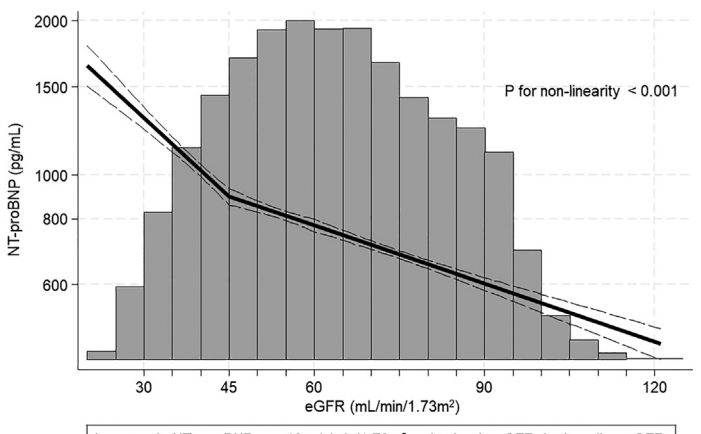


eGFR (mL/min/1.73m²)	NT-proBNP (pg/mL)
≥60	701 (357-1279)
45-<60	945 (501-174)
<45	1250 (631-2312)

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

outcome and hospitalization for heart failure when accounting for competing risk of noncardiovascular death and all-cause death, respectively (sub-HR: 1.36 [95% CI: 1.32-1.40]; and sub-HR: 1.32 [95% CI: 1.27-1.37]). At any given concentration of NT-proBNP, the relative risk of adverse outcomes was notably higher for participants with eGFR <45 mL/min/1.73 m². The association of eGFR and NT-proBNP, separately, with clinical outcomes is displayed in Supplemental Figures 1 and 2.

FIGURE 2 Association Between eGFR and NT-proBNP



Increase in NT-pro-BNP per 10 mL/min/1.73m² reduction in eGFR, by baseline eGFR		
<45	45-<60	≥60
23% (18-27)	8% (4-11)	9% (7-10)

Abbreviations as in Figure 1.

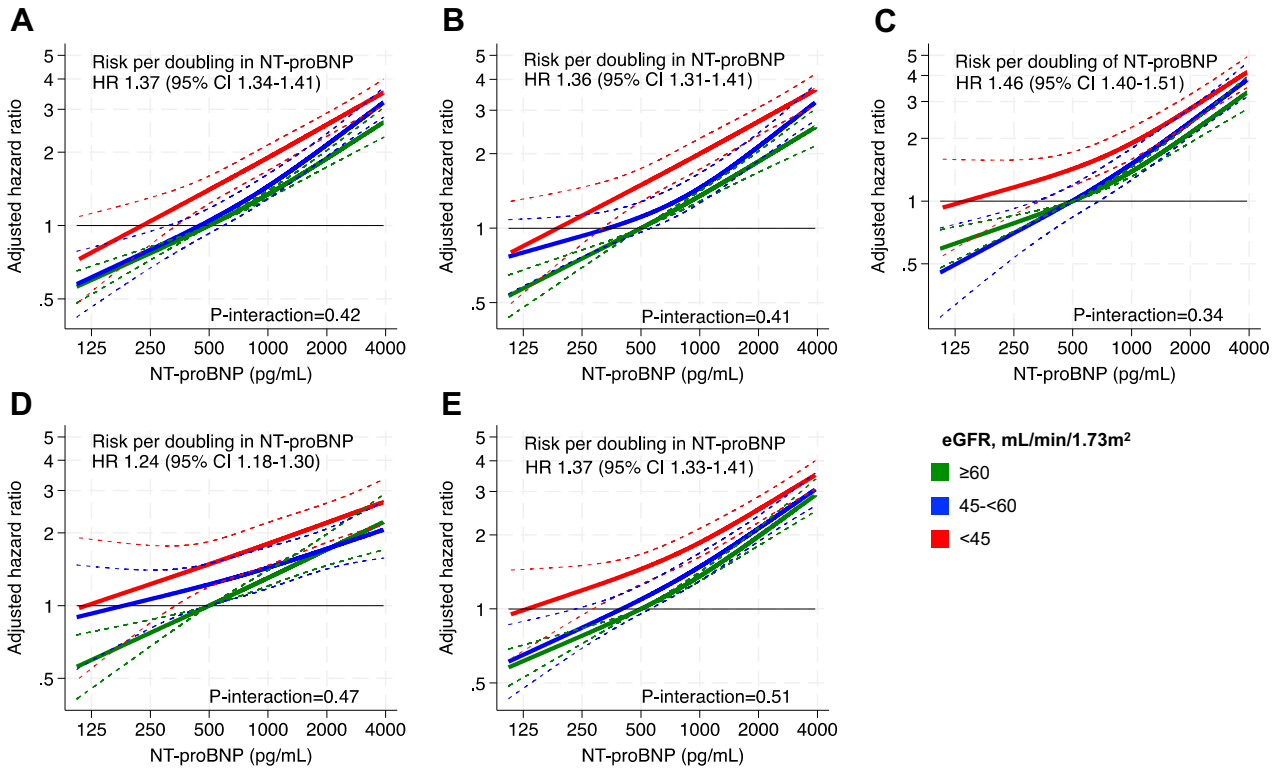
Incidence rates for the primary outcome across different levels of NT-proBNP, stratified by eGFR, are displayed in **Figure 4**. For participants with eGFR ≥60 mL/min/1.73 m², an NT-proBNP level of 1,946 pg/mL corresponded to an absolute risk of 10 per 100 patient-years. For participants with eGFR of 45 to <60 and <45 mL/min/1.73 m², the corresponding NT-proBNP levels were 1,457 and 756 pg/mL respectively, reflecting an almost 3-fold difference for eGFR ≥60 compared with <45 mL/min/1.73 m² for the same absolute risk (**Central Illustration**). NT-proBNP levels corresponding to an absolute risk of 5 per 100 patient-years were 438, 332, and 118 pg/mL for participants with eGFR ≥60, 45 to <60, and <45 mL/min/1.73 m², respectively—again exposing an approximate 3.5-fold variation in NT-proBNP level for the same absolute risk (**Central Illustration**). A similar pattern of association was observed for other outcomes, although the absolute risk gradient for NT-proBNP was shallower for noncardiovascular compared with cardiovascular death (**Figure 4**). Graded increases in incidence of all outcomes were observed across lower categories of eGFR and higher categories of NT-proBNP (**Figure 5**).

The pattern of association for NT-proBNP and absolute risk of the primary outcome was similar in subgroup analyses by age, sex, diabetes status, BMI, and history of atrial fibrillation (Supplemental Figure 3). Results were also consistent in sensitivity analyses adjusting for the mean age, mean BMI, and prevalence of atrial fibrillation in the overall population (Supplemental Table 2).

DISCUSSION

In this pooled individual participant data analysis of 4 large-scale randomized trials in persons with heart failure with mildly reduced or preserved ejection fraction, we made several important observations regarding the relationship between NT-proBNP, kidney function, and clinical outcomes. First, although NT-proBNP levels were higher with lower kidney function, the association is nonlinear and more pronounced in patients with eGFR <45 mL/min/1.73 m². Second, in relative and absolute terms, associations between NT-proBNP and risk of adverse outcomes are consistent across different levels of kidney function. Third, because kidney function also independently predicts risk of heart failure outcomes, for any given NT-proBNP concentration, the absolute risk of adverse outcomes is substantially higher for patients with reduced kidney function compared with those

FIGURE 3 Associations of NT-proBNP With Clinical Outcomes by Baseline eGFR



Association of NT-proBNP with hospitalization for heart failure or cardiovascular death (A), hospitalization for heart failure (B), cardiovascular death (C), noncardiovascular death (D), and all-cause mortality across different levels of eGFR (E). Abbreviations as in Figure 1.

with preserved kidney function. These data suggest that revising upper reference limits for NT-proBNP in patients with CKD may risk overlooking valuable prognostic information, and that reduced kidney function per se should not be a reason to disregard higher NT-proBNP levels.

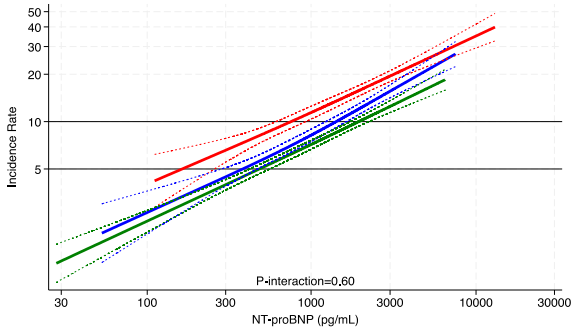
Although it is recognized that NT-proBNP levels are higher in persons with CKD, how this impacts its relationship with clinical outcomes has been incompletely characterized. In the Chronic Renal Insufficiency Cohort, the proportion of individuals with CKD who had an NT-proBNP level >125 pg/mL was progressively higher across lower eGFR categories such that 71% of patients with eGFR <30 mL/min/1.73 m^2 had an NT-proBNP level >125 pg/mL.[17] In the general population, elevated NT-proBNP levels consistently predicted the risk of cardiovascular death and all-cause mortality across different levels of kidney function.[18] We confirm and extend these insights to patients with heart failure with mildly reduced or preserved ejection fraction, demonstrating a nonlinear relationship between NT-proBNP and eGFR and consistent relative and absolute risk gradient for many adjudicated outcomes.

Because NT-proBNP concentrations are generally higher in patients with CKD, there has been some suggestions to revise the upper reference limits for NT-proBNP using eGFR-specific reference values, acknowledging that most patients with advanced CKD will have elevated NT-proBNP concentrations based on currently accepted thresholds.[17] Our data indicate these individuals face markedly higher absolute risk of heart failure outcomes compared with patients with the equivalent NT-proBNP concentration but normal kidney function. As such, our findings suggest caution regarding proposals for higher upper reference limits for NT-proBNP in patients with CKD because such changes may risk overlooking valuable prognostic information.

The observed association between NT-proBNP and eGFR can be attributed to multiple mechanisms. First, peptide accumulation due to reduced filtration is likely a modest contributor because the relative difference between the arterial concentration and the

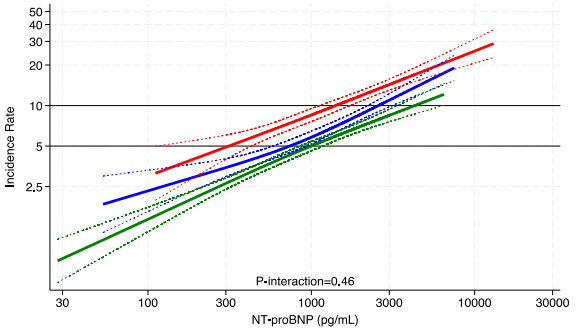
FIGURE 4 Incidence Rates per 100 Patient-Years for Clinical Outcomes by Baseline NT-proBNP and eGFR

A HHF or CV death



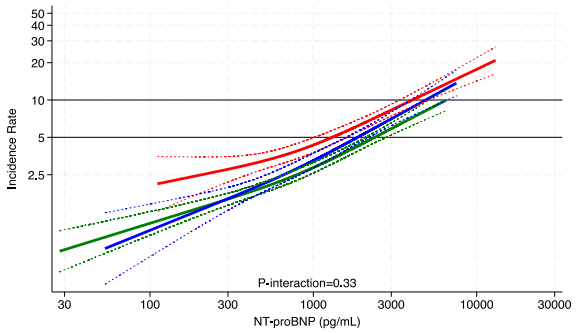
eGFR (mL/min/1.73m²)	NT-proBNP (pg/mL) at **5** events per 100 patient-yrs	NT-proBNP (pg/mL) at **10** events per 100 patient-yrs
≥60	438	1946
45-<60	332	1457
<45	118	756

B HHF



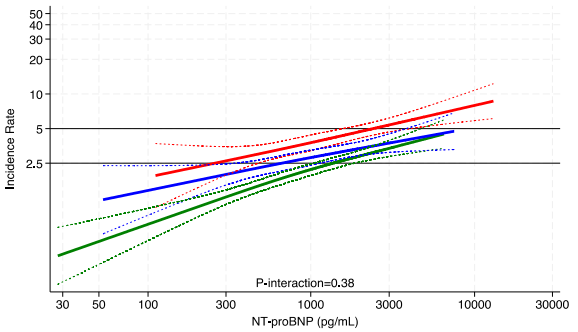
eGFR (mL/min/1.73m²)	NT-proBNP (pg/mL) at **5** events per 100 patient-yrs	NT-proBNP (pg/mL) at **10** events per 100 patient-yrs
≥60	981	4177
45-<60	717	2566
<45	285	1422

C CV death



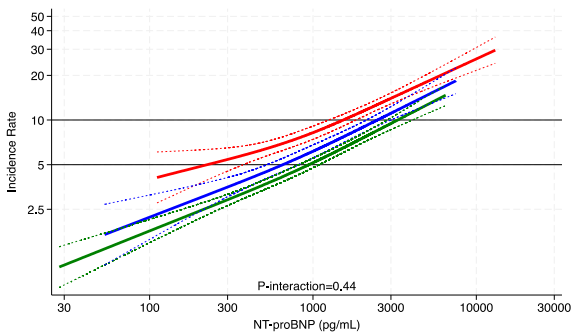
eGFR (mL/min/1.73m²)	NT-proBNP (pg/mL) at **5** events per 100 patient-yrs	NT-proBNP (pg/mL) at **10** events per 100 patient-yrs
≥60	2345	6202
45-<60	1922	4746
<45	1375	4000

D Non-CV death



eGFR (mL/min/1.73m²)	NT-proBNP (pg/mL) at **5** events per 100 patient-yrs	NT-proBNP (pg/mL) at **10** events per 100 patient-yrs
≥60	1256	8952
45-<60	652	8303
<45	291	2002

E All-cause death

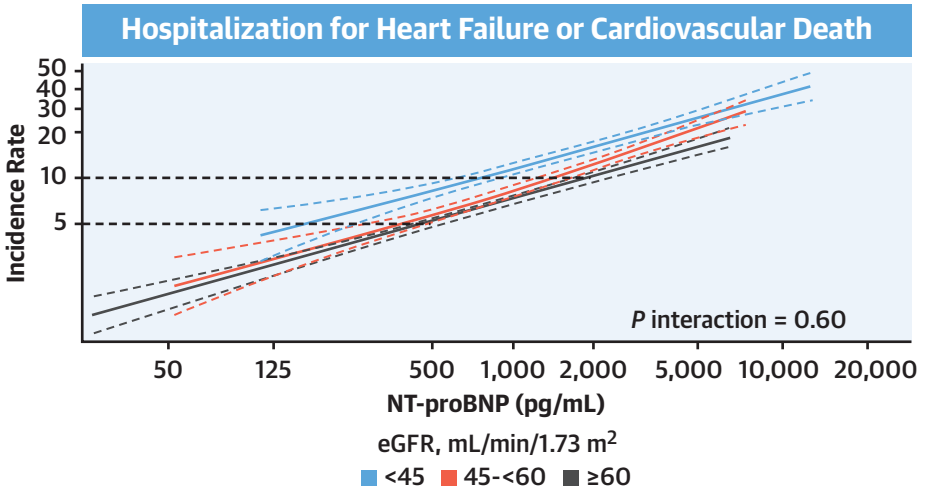


eGFR (mL/min/1.73m²)	NT-proBNP (pg/mL) at **5** events per 100 patient-yrs	NT-proBNP (pg/mL) at **10** events per 100 patient-yrs
≥60	957	3293
45-<60	673	2527
<45	158	1573

eGFR, mL/min/1.73m²
- ≥60
- 45-<60
- <45

Incidence rates for hospitalization for heart failure or CV death (A), hospitalization for heart failure (B), CV death (C), non-CV death (D), and all-cause mortality by baseline continuous NT-proBNP (E), stratified by eGFR. CV = cardiovascular; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Incidence of Hospitalization for Heart Failure or Cardiovascular Death According to NT-proBNP and eGFR**



eGFR (mL/min/1.73 m^2)	NT-proBNP (pg/mL) at 5 Events Per 100 Patient-Years	NT-proBNP (pg/mL) at 10 Events Per 100 Patient-Years
≥60	438	1,946
45-<60	332	1,457
<45	118	756

Neuen BL, et al. JACC Heart Fail. 2025;13(1):28–39.

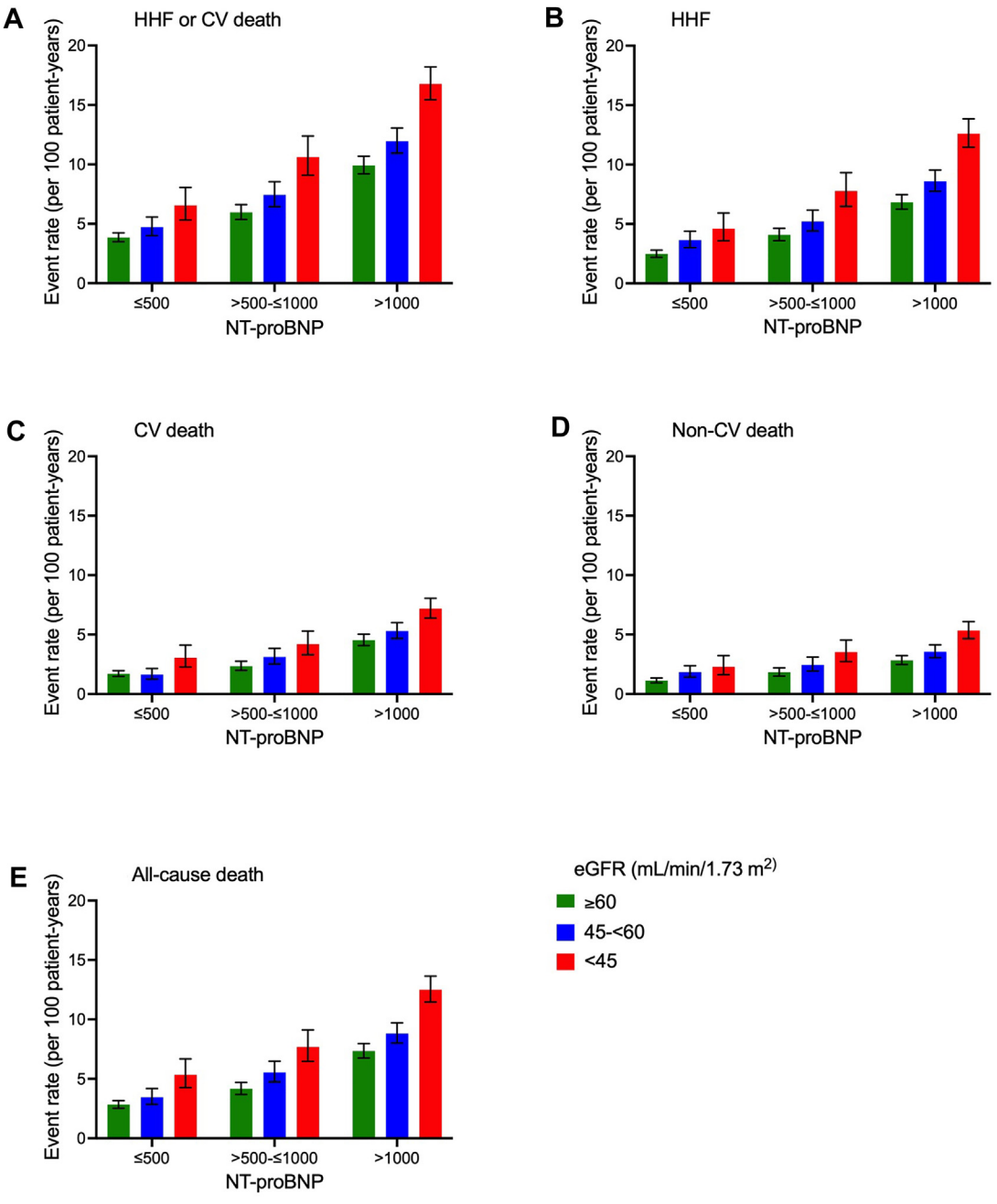
eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

venous concentration of BNP and NT-proBNP shows only a weak correlation with glomerular filtration rate (r = ~0.20).[5] More significant is the increased expression of NT-proBNP by cardiomyocytes, driven by shared comorbidities such as hypertension, left ventricular hypertrophy, and chronic volume overload.[19] Additionally, activation of the renin-angiotensin system—a key feature in both heart failure and chronic kidney disease—serves as a potent stimulus for natriuretic peptide production as a counter-regulatory mechanism.[20] Our observation that the relationship between NT-proBNP and eGFR is nonlinear, such that 10-U reductions in eGFR were associated with greater increases in NT-proBNP at lower starting eGFR, is consistent with similar analyses in the general population.[18]

The data strongly support the prognostic utility of NT-proBNP in heart failure across all levels of kidney function studied, and that reduced kidney function per se should not be a reason to disregard higher NT-proBNP levels. Indeed, those with eGFR <45 mL/min/1.73 m^2 with higher levels of NT-proBNP are at highest absolute risk of adverse clinical outcomes. Recognizing this is critically important for the appropriate interpretation of NT-proBNP because CKD is one of the most common comorbidities in patients with heart failure. Conversely, comparatively lower NT-proBNP levels in patients with heart failure and CKD, especially those with eGFR <45 mL/min/1.73 m^2, may not adequately capture absolute risk of worsening heart failure. Indeed, the NT-proBNP levels corresponding to an absolute risk of 5 events per 100 patient-years was <125 pg/mL for patients with eGFR <45 mL/min/1.73 m^2—approximately 3.5-fold lower than for patients with normal kidney function who experienced the same cardiovascular event rate.

Our findings may also have implications for the design and conduct of heart failure trials. Contemporary trials in heart failure with mildly reduced or preserved ejection fraction have used NT-proBNP as an enrichment strategy to ensure participants enrolled are at sufficient risk to achieve the requisite number of events. NT-proBNP entry criteria have typically considered atrial fibrillation and history of heart failure hospitalization, but not other comorbidities that might impact NT-proBNP levels, such as CKD. Our findings raise the possibility that less

FIGURE 5 Incidence Rates per 100 Patient-Years According to Combined Categories of NT-proBNP and eGFR



Incidence rates for HHF or CV death (A), HHF (B), CV death (C), non-CV death (D), and all-cause mortality (E) by categories of baseline NT-proBNP and eGFR. HHF = hospitalization for heart failure; other abbreviations as in Figures 1 and 4.

stringent NT-proBNP entry criteria for patients with concomitant CKD, especially those with eGFR <45 mL/min/1.73 m^2, might facilitate recruitment without affecting event rates, although this hypothesis would need to be tested prospectively.

In comparison to heart failure outcomes, there is relatively little data on the relationship between NT-proBNP and noncardiovascular outcomes. This is particularly relevant for patients with heart failure with mildly reduced or preserved ejection fraction for whom the competing risk of noncardiovascular death is often higher than those with heart failure with reduced ejection fraction.[21] We observed that although NT-proBNP levels also predict noncardiovascular death, the absolute risk gradient for this outcome was less steep compared with cardiovascular death. Our results are consistent with and extend previous findings in patients with reduced ejection fraction.[22]

STUDY LIMITATIONS. These analyses represent one of the largest and most comprehensive assessments of the relationship between NT-proBNP, kidney function, and clinical outcomes in patients with heart failure with mildly reduced or preserved ejection fraction. Analyses were conducted in a well-phenotyped population enrolled from 4 well-conducted randomized trials with complete data and a large number of adjudicated clinical outcomes. However, some limitations should be recognized when interpreting these findings. Despite careful multivariable adjustment, residual confounding may impact the described associations between NT-proBNP and clinical outcomes. The equivalent NT-proBNP levels corresponding to specific cardiovascular event rates across different levels of kidney function reflect the characteristics of the population studied and may not be generalizable to all patients with heart failure with mildly reduced or preserved ejection fraction. Nevertheless, the cohort represents a well-treated group of patients whose characteristics broadly reflect those of contemporary heart failure trials, and subgroup analyses by various characteristics as well as adjustment for those factors known to influence NT-proBNP levels support the robustness of our conclusions. Finally, there were very few participants with eGFR <30 mL/min/1.73 m^2 and thus we were unable to draw conclusions about these individuals.

Further work to better understand the prognostic utility of NT-proBNP for cardiovascular, kidney and mortality outcomes in patients with CKD who do not have established heart failure is a critically important topic that warrants further study in dedicated CKD cohorts. Such studies may be able to address optimal lower threshold of NT-proBNP to rule out a diagnosis of heart failure. This may be particularly important for 2 reasons. First, clinical practice guidelines such as those from the American Diabetes Association increasingly recommend that NT-proBNP be measured annually to screen for heart failure in persons with diabetes, many of whom will have CKD and benefit from therapies that prevent worsening heart failure.[23,24] Second, in persons with CKD, NT-proBNP has been proposed as a safety biomarker for the use of endothelin receptor antagonists, which are likely to protect the kidney but also cause fluid retention and potentially increase the risk of worsening heart failure.[25,26] Understanding these issues will be necessary for the more widespread use of NT-proBNP for diagnosis and risk stratification in persons with CKD who are often at risk of but have yet not been diagnosed or developed clinical heart failure.

CONCLUSIONS

The same NT-proBNP concentration predicts a substantially higher absolute risk of adverse outcomes for people with heart failure and reduced kidney function, compared with those with preserved kidney function. These data call into question proposals for higher NT-proBNP references ranges in people with CKD, and suggest that reduced kidney function per se should not be a reason to disregard higher NT-proBNP levels.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: NT-proBNP is a potent predictor of heart failure outcomes across the spectrum of kidney function. However, the same NT-proBNP concentration predicted a substantially higher absolute risk of adverse outcomes for people with heart failure and reduced kidney function, compared with those with preserved kidney function.

TRANSLATIONAL OUTLOOK: These results call into question proposals to revise the upper reference limits for NT-proBNP using eGFR-specific reference values, emphasizing that reduced kidney function per se should not be a reason to disregard higher NT-proBNP levels, and that doing so may risk overlooking valuable prognostic information.

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KEY WORDS chronic renal insufficiency, glomerular filtration rate, heart failure, kidney, natriuretic peptides, N-terminal pro-B-type natriuretic peptide, treatment outcome

APPENDIX For supplemental figures and tables, please see the online version of this paper.

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