

B-Type Natriuretic Peptide Predicts 30-Day Readmission for Heart Failure but not Readmission for Other Causes

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Background—B-type natriuretic peptide (BNP) is a marker for heart failure (HF) severity, but its association with hospital readmission is not well defined.

Methods and Results—We identified all hospital discharges (n=109 875) with a primary diagnosis of HF in the Veterans Affairs Health Care System from 2006 to 2009. We examined the association between admission (n=53 585), discharge (n=24 326), and change in BNP (n=7187) and 30-day readmission for HF or other causes. Thirty-day HF readmission was associated with elevated admission BNP, elevated discharge BNP, and smaller percent change in BNP from admission to discharge. Patients with a discharge BNP ≥ 1000 ng/L had an unadjusted 30-day HF readmission rate over 3 times as high as patients whose discharge BNP was ≤ 200 ng/L (15% vs. 4.1%). BNP improved discrimination and risk classification for 30-day HF readmission when added to a base clinical model, with discharge BNP having the greatest effect (C-statistic, 0.639 to 0.664 [$P < 0.0001$]; net reclassification improvement, 9% [$P < 0.0001$]). In contrast, 30-day readmission for non-HF causes was not associated with BNP levels during index HF hospitalization.

Conclusions—In this study of over 50 000 veterans hospitalized with a primary diagnosis of HF, BNP levels measured during hospitalization were associated with 30-day HF readmission, but not readmissions for other causes. These data may help guide future study aimed at identifying the optimal timing for hospital discharge and help allocate high-intensity, HF-specific transitional care interventions to the patients most likely to benefit. (*J Am Heart Assoc.* 2014;3:e000806 doi: 10.1161/JAHA.114.000806)

Key Words: heart failure • natriuretic peptides • patient readmission • prognosis

In the United States, patients hospitalized with a primary diagnosis of heart failure (HF) have a 30-day all-cause readmission rate of 12% to 27%,¹⁻⁴ resulting in significant cost to the healthcare system and diminished quality of life. Unfortunately, efforts at predicting readmission among patients hospitalized for HF have produced heterogeneous results and generally have not been as successful as those aimed at predicting mortality.^{1,2,5-7} Novel methods for characterizing HF patients' risk of hospital readmission are necessary to improve the care of this vulnerable patient population.

Natriuretic peptides, such as B-type natriuretic peptide (BNP), are released from cardiomyocytes in response to pressure or volume-overloaded states and are a marker of HF severity.⁸ The use of natriuretic peptides in the diagnosis of acutely decompensated HF is well established.⁹⁻¹¹ Natriuretic peptides have also been shown to predict both mortality and readmission in a variety of settings¹²⁻²⁷; however, the majority of these studies were small, single center, and did not evaluate hospital readmission separate from mortality. Therefore, the aim of the current study was to examine the association between admission, discharge, and percent change in BNP levels from admission to discharge with 30-day hospital readmission in a large, national cohort of patients within the Veterans Affairs (VA) Health Care System.

Methods

Patients and BNP Measurements

Using deidentified data in the national VA Health Care System database, we identified all patients discharged from a VA hospital with a primary diagnosis of HF between 2006 and 2009. According to institutional policy, the current study did

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not require institutional review board approval. Patients were considered to have a comorbid illness (ie, diabetes, hypertension [HTN], coronary artery disease [CAD], stroke and chronic obstructive pulmonary disease [COPD]) if they had been treated for the condition in the 2 years preceding the index admission. Baseline laboratory values (sodium, creatinine, and hemoglobin) were defined as the value within the preceding 6 months that was closest to the day of admission. Patients who died within 30 days of admission were excluded from all readmission analyses.

We examined 3 different strategies for assessing BNP: admission levels; discharge levels; and the percent change in BNP levels from admission to discharge. Admission BNP was defined as any BNP value measured on or within 3 days before admission. Discharge BNP was defined as any BNP value measured on or within the 2 days before discharge during a hospital stay lasting >2 days. When multiple BNP measurements met criteria for either admission or discharge BNP, the average was taken. Percent change in BNP from admission to discharge was limited to hospital stays that were longer than 2 days and during which both an admission and discharge BNP were measured. Given the infrequent use of NT-proBNP in the VA population, we limited our analyses to BNP testing.

Outcome

The main outcomes for this study were 30-day all-cause readmission, 30-day HF readmission, and 30-day readmission for other causes. We were particularly interested in the differential impact of BNP on HF and non-HF readmission. Readmission data were limited to hospitalizations paid for by the VA (includes some non-VA hospitalizations). Secondary outcomes included inpatient and 30-day all-cause mortality. Thirty-day outcomes were available for 98.4% of patients (n=108 079 of a total of 109 875). For mortality analyses, we included only the first hospitalization for patients admitted multiple times. The primary analysis of the association between BNP and readmission used unique hospitalizations as the unit of analysis. In sensitivity analyses, we included only the first admission per patient.

Statistics

Patient characteristics are reported as mean±SD. Differences in patient characteristics between those who did and did not have a BNP measured were assessed using the Student *t* test. The unadjusted association between index admission BNP levels (admission BNP, discharge BNP, and percent change in BNP from admission to discharge) and outcomes (30-day all-cause readmission, 30-day HF readmission, 30-day readmission for other causes, and inpatient and 30-day mortality)

were assessed using the chi-square test. Logistic regression models were created for each BNP measurement strategy to assess the association of BNP with 30-day HF readmission after adjustment for demographics (age, black race, and gender), year hospitalized, history of diabetes, HTN, CAD, COPD, stroke, and serum sodium, creatinine, and hemoglobin (base clinical model). In sensitivity analyses, we adjusted for clustering of admissions by patient and facility using generalized estimating equations.

We evaluated discrimination and net reclassification for each BNP strategy utilizing the subset of patients with both admission and discharge BNP data available. Results of logistic regression with and without BNP values were compared to determine the impact of BNP on the area under the receiver operating characteristic curve and the net reclassification improvement (NRI). To determine NRI, we created the following classifications for 30-day all-cause, HF, and non-HF readmission rates: very low (all cause <10%, HF <4%, and non-HF <5%), low (all cause 10% to 19%, HF 4% to 7%, and non-HF 5% to 9%), moderate (all cause 20% to 29%, HF 8% to 11%, and non-HF 10% to 14%), and high (all cause ≥30%, HF specific ≥12%, and non-HF ≥15%). We then analyzed the net number of patients correctly reclassified to a higher or lower risk category when admission, discharge, or change in BNP was added to the base clinical model and, from that, calculated the NRI.²⁸

For multivariate analyses, we created a separate category of missing (indicator variable) for those categorical variables with missing data. For example, history of diabetes was coded as either present, absent, or missing. Missing continuous variables were imputed using the mean value. There were no missing values for age, sex, and year hospitalized. History of diabetes, stroke, HF, COPD, HTN, and CAD was missing in 5.8% of the hospitalizations studied. Race was missing in 8.5% of hospitalizations, and creatinine, hemoglobin, and sodium were missing in 14%, 13%, and 8.7% of hospitalizations, respectively. A *P* value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software (version 9.0; SAS Institute Inc., Cary, NC).

Results

Between 2006 and 2009, there were 109 875 admissions with a principle diagnosis of HF documented among 67 094 patients across 125 VA hospitals. A measurement of natriuretic peptide was obtained in over half of admissions, and the majority of levels were BNP (n=55 759; 51%), rather than NT-proBNP (n=4 137; 3.7%). There were no clinically relevant differences in baseline clinical characteristics (Table 1) or 30-day readmission outcomes (data not shown) among patients with and without BNP testing during their hospitalization.

Table 1. Patient Characteristics

Baseline Characteristic	All Patients With BNP Measured (N=55 759)	Admission BNP (N=53 585)	Discharge BNP (N=24 326)	Admission and Discharge BNP; LOS>2 days (N=7187)	Natriuretic Peptide Not Measured (N=54 116)
Age, y (mean±SD)	71±12	71±12	71±12	71±12	69±12
Male, N (%)	54 789 (98)	52 659 (98)	23 928 (98)	7075 (98)	53 074 (98)
Black, N (%)	12 591 (24)	12 370 (25)	5621 (25)	1577 (23)	14 453 (30)
Coronary artery disease, N (%)	44 666 (83)	42 858 (83)	19 571 (83)	5790 (83)	40 897 (83)
Hypertension, N (%)	51 262 (95)	49 217 (95)	22 367 (95)	6591 (95)	46 676 (94)
Diabetes, N (%)	36 981 (68)	35 355 (68)	15 748 (67)	4830 (70)	32 991 (67)
Cerebrovascular disease, N (%)	25 954 (48)	24 802 (48)	10 821 (46)	3420 (49)	22 376 (45)
Chronic obstructive pulmonary disease, N (%)	38 966 (72)	37 223 (72)	16 609 (71)	5133 (74)	34 614 (70)
Sodium, mmol/L (mean±SD)	138±4.1	138±4.1	138±4.0	138±4.3	138±4.0
Creatinine, μmol/L (mg/dL) (mean±SD)	155.6±114.9 (1.76±1.3)	155.6±114.9 (1.76±1.3)	152.1±114.9 (1.72 ± 1.3)	156.5±97.2 (1.77±1.1)	160.0±141.4 (1.81 ± 1.6)
Hemoglobin, g/L (g/dL) (mean±SD)	119±20 (11.9±2.0)	119±20 (11.9±2.0)	120±20 (12.0±2.0)	119±20 (11.9±2.0)	120±21 (12.0±2.1)

BNP indicates B-type natriuretic peptide. Denominator for race is the following: any BNP 52 452, admission 50 342, discharge 22 933, both 6787, and no BNP 48 074. Denominator for comorbidities is the following: any BNP 53 955, admission 51 806, discharge 23 524, both 6944, and no BNP 49 482. Sample size for lab data for any BNP 54 073, admission 51 988, discharge 24 966, both 7376, and no BNP 40 396. LOS indicates length of stay.

BNP Level and Readmission

Admission BNP was measured in 53 585 patients (49%), and discharge BNP was measured in 24 326 (22%). A minority of patients (n=7 187; 6.5%) had both an admission and discharge BNP measured. Figure 1 shows the distribution of admission BNP values, discharge BNP values, and the percent change in BNP from admission to discharge. Notably, 43% of patients with a discharge BNP had a value ≥ 1000 ng/L. Mean BNP levels did not differ significantly between those with only an admission BNP or only a discharge BNP measured and those who had both values measured (data not shown).

Admission, discharge, and percent change in BNP were all correlated with 30-day HF readmission and 30-day all-cause readmission (Figure 2). The risk of 30-day HF readmission increased in a linear fashion as both admission and discharge BNP rose from 200 to 1000 ng/L and was over 3 times higher in patients whose discharge BNP was ≥ 1000 ng/L versus BNP < 200 ng/L.

Adjusted Associations and Incremental Discrimination

The association between each BNP measurement strategy and 30-day HF readmission persisted after controlling for variables in the base clinical model (Figure 3). Odds ratios (ORs) for the other variables included in these models are shown in Table 2. Because of the significant difference in cohort sizes for admission, discharge, and change in BNP, we

compared the discrimination and NRI for each measurement strategy in the 7187 patients with both admission and discharge BNP available (Table 3). Of the 3 BNP measurement strategies, discharge BNP conferred the greatest increase in discrimination and net reclassification. When the full cohort for discharge BNP (n=24 326) was analyzed, discharge BNP once again improved both discrimination and net reclassification for 30-day HF readmission and 30-day all-cause readmission when added to the base clinical model (C-statistic from 0.645 to 0.672 [$P<0.0001$] and 0.621 to 0.628 [$P<0.0001$], respectively; NRI 10.6% [$P<0.0001$] and 3.7% [$P<0.0001$], respectively). Accordingly, when the full cohort for admission BNP (n=53 585) was included, the C-statistic and NRI also increased for 30-day HF and all-cause readmission (C-statistic from 0.643 to 0.653 [$P<0.0001$] and 0.616 to 0.619 [$P<0.0001$], respectively; NRI 5% [$P<0.001$] and 1% [$P=0.004$], respectively).

In contrast to readmission for HF, readmission for other causes was not associated with admission, discharge, or percent change in BNP (Figure 2), even after adjustment for the base clinical model (Table 3). There was no appreciable change in C-statistic or NRI for 30-day readmissions for causes other than HF when the full cohorts for either discharge or admission BNP were used (data not shown).

Sensitivity Analyses

When we included only the first admission per patient, the overall admission rate was lower, but the association with

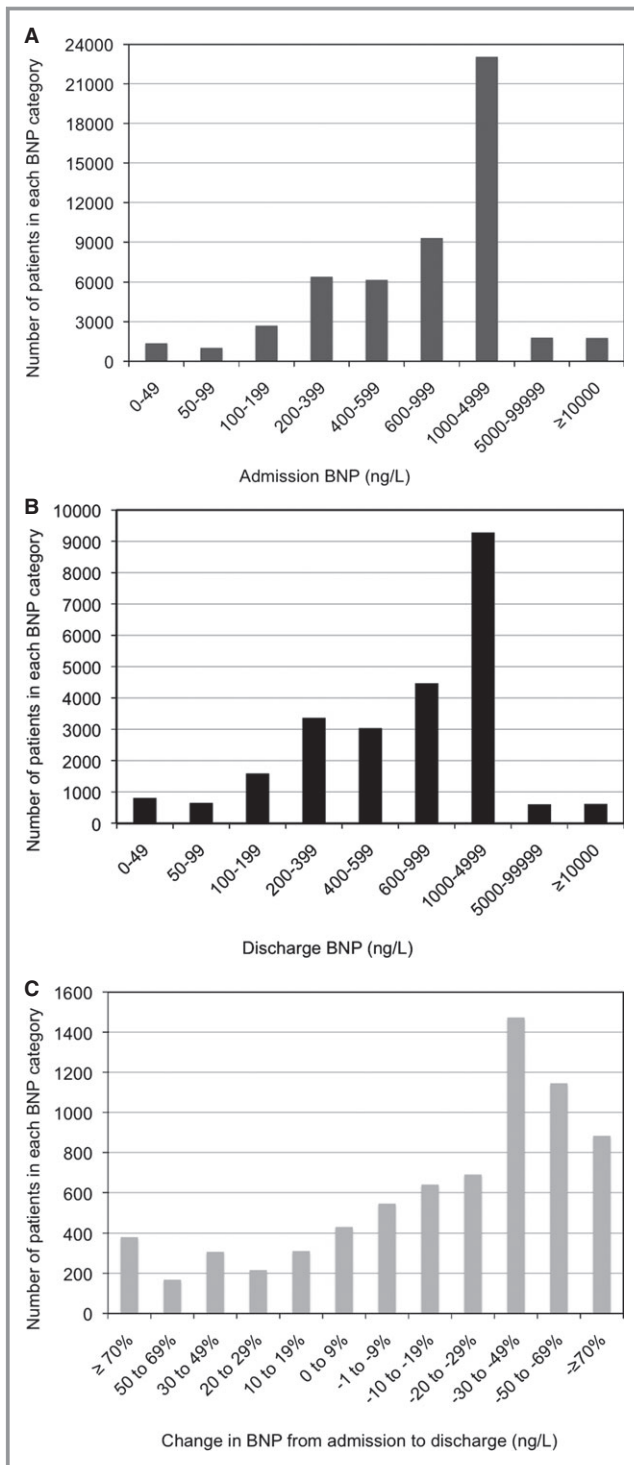


Figure 1. Distribution of (A) admission BNP (N=53 585), (B) discharge BNP (N=24 326), and (C) percent change in BNP (N=7187) from admission to discharge. BNP indicates B-type natriuretic peptide.

BNP was not substantially different. In analyses that controlled for clustering of admissions by patient or within hospitals, the confidence intervals (CIs) widened, but the

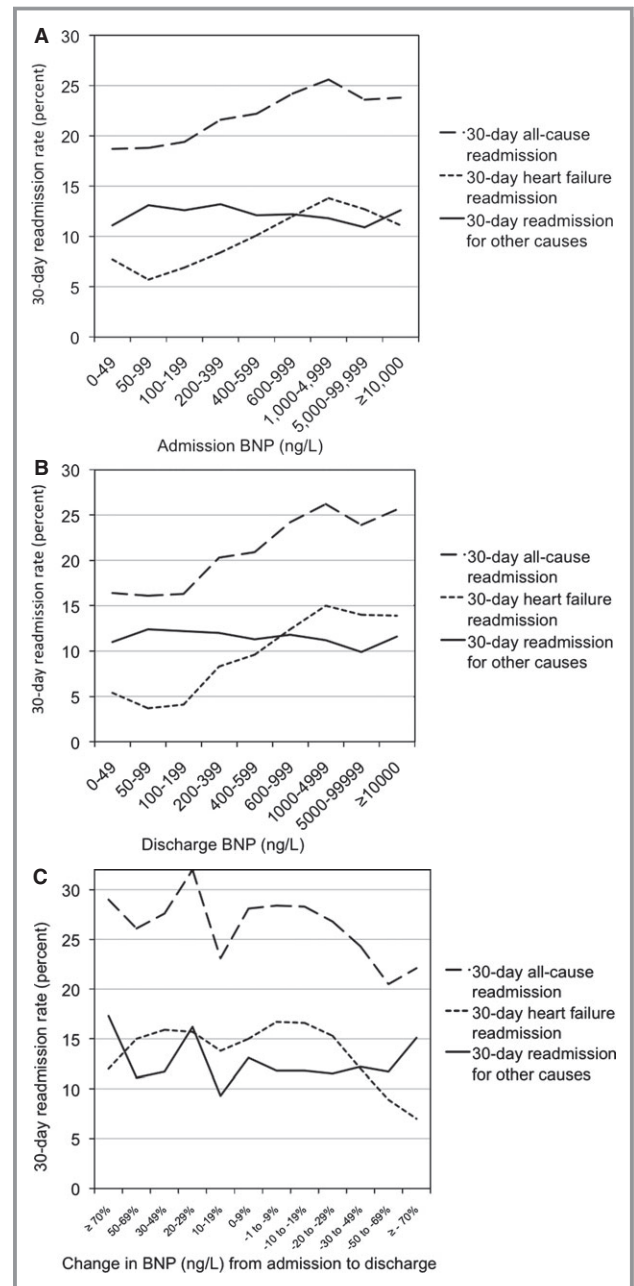


Figure 2. A, Percentage of patients in each admission BNP category who met the following outcomes: 30-day all-cause, heart failure (HF), and non-HF readmission. $P<0.0001$ for unadjusted 30-day all-cause and HF readmission rates; $P=0.0495$ for unadjusted 30-day readmission for other causes; BNP, B-type natriuretic peptide; N=53 585. B, Percentage of patients in each discharge BNP category who met the following outcomes: 30-day all-cause, HF, and non-HF readmission. $P<0.0001$ for unadjusted 30-day all-cause and HF-specific readmission rates; $P=0.7265$ for unadjusted 30-day readmission for other causes; BNP, B-type natriuretic peptide; N=24 326. C, Percentage of patients in each change in BNP category who met the following outcomes: 30-day all-cause, HF, and non-HF readmission. $P=0.0002$ for unadjusted 30-day all-cause readmission; $P<0.0001$ for unadjusted 30-day HF readmission; $P=0.0879$ for unadjusted 30-day readmissions for other causes; BNP, B-type natriuretic peptide; N=7187.

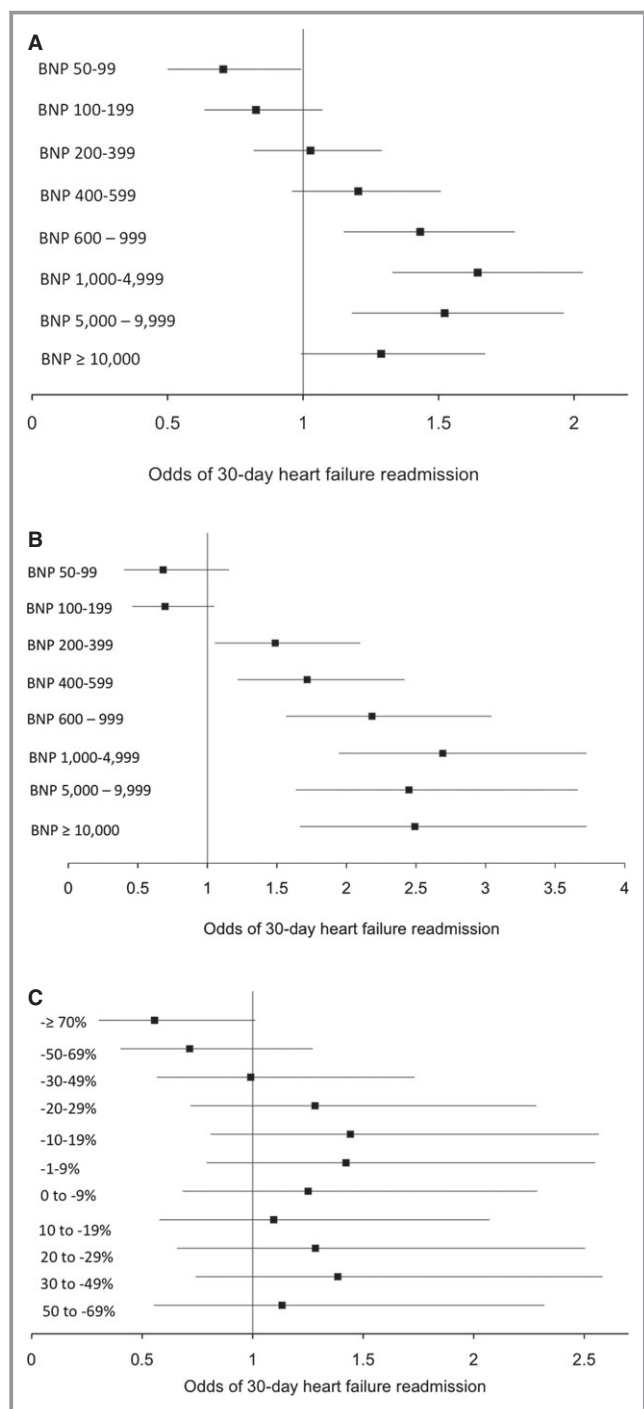


Figure 3. A, Forest plot of admission BNP categories (N=53 585; using the 0 to 49 category as a reference) and 30-day heart failure (HF) readmission. B, Forest plot of discharge BNP categories (N=24 326; using the 0 to 49 category as a reference) and 30-day HF readmission. C, Forest plot of percent change in BNP from admission to discharge categories (N=7187; using the $\geq 70\%$ category as a reference) and 30-day HF readmission; BNP, B-type natriuretic peptide; BNP effect is adjusted for the base clinical model (demographics [age, black race, and gender], year hospitalized, history of diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, stroke, and serum sodium, creatinine, and hemoglobin).

overall effect of BNP on predicting readmission remained highly significant. For example, the OR for 30-day HF readmission with a discharge BNP of 1000 to 4999 ng/L versus 0 to 49 ng/L, was 2.69 (95% CI, 1.96 to 3.72; Figure 3B). With controls for clustering of admissions within patients or hospitals, the 95% CI increased to 1.92 to 3.78 and 1.51 to 4.79, respectively.

Mortality

A total of 1846 (2.8%) patients died during hospitalization, and 3185 (4.8%) died within 30 days after admission. Higher BNP levels at admission and preceding discharge were associated with higher mortality rates. Thirty-day mortality was 2.7% if discharge BNP was <200 ng/L and 8.8% if the discharge BNP was >5000 ng/L. After adjustment for the base clinical model, higher admission BNP levels remained significantly associated with higher inpatient mortality ($P<0.0001$). Similarly, higher discharge BNP levels were associated with greater 30-day mortality ($P<0.0001$). Admission, discharge, and change in BNP all added incremental value to the base clinical model in predicting all-cause mortality (C-statistic from 0.711 to 0.717 [$P=0.08$], 0.735 [$P=0.0005$], and 0.752 [$P<0.0001$], respectively; NRI 3.7% [$P=0.047$], 10.6% [$P=0.002$], and 19.3% [$P<0.0001$]) in the 7187 patients who had both admission and discharge BNP available. These results did not change appreciably when the full cohort for admission or discharge BNP were used (C-statistic from 0.694 to 0.706 [$P<0.0001$] and 0.704 to 0.721 [$P<0.0001$], respectively; NRI 6.4% [$P<0.0001$] and 6.9% [$P>0.0001$]).

Discussion

This large, population-based study of patients hospitalized with a primary diagnosis of HF demonstrated that admission, discharge, and percent change in BNP levels from admission to discharge were all associated with 30-day HF readmission, but not with 30-day readmission for other causes. This association persisted after adjustment for potential confounders. All 3 BNP measurement strategies provided incremental improvement in discrimination and net reclassification when added to usual predictor variables, with discharge BNP having the largest effect size. Patients whose admission or discharge BNP was ≥ 1000 ng/L were 2 to 3 times more likely to be readmitted for HF in 30 days, compared to those with admission or discharge BNP levels <200 ng/L. This effect was most notable for discharge BNP. Finally, both admission and discharge BNP were associated with inpatient and 30-day mortality, with higher BNP levels conferring a greater risk of death.

Table 2. Odds Ratios for Basic Clinical and Demographic Variables Included in the Adjusted Logistic Regression Analyses for Admission, Discharge, and Change in BNP and 30-Day Heart Failure Readmission

	Admission BNP Odds Ratio (95% CI)	Discharge BNP Odds Ratio (95% CI)	Change in BNP Odds Ratio (95% CI)
Age	0.987 (0.985 to 0.990)	0.988 (0.985 to 0.992)	0.988 (0.982 to 0.995)
Female	0.652 (0.501 to 0.847)	0.681 (0.460 to 1.009)	0.621 (0.298 to 1.295)
Race (nonblack vs. missing)	1.264 (1.033 to 1.547)	1.026 (0.764 to 1.379)	0.986 (0.567 to 1.715)
Race (black vs. missing)	1.646 (1.339 to 2.024)	1.431 (1.059 to 1.934)	1.451 (0.825 to 2.554)
Year hospitalized (2006 vs. 2009)	1.018 (0.935 to 1.109)	0.958 (0.843 to 1.090)	0.981 (0.767 to 1.253)
Year hospitalized (2007 vs. 2009)	1.006 (0.928 to 1.091)	0.923 (0.819 to 1.040)	1.118 (0.903 to 1.385)
Year hospitalized (2008 vs. 2009)	0.982 (0.909 to 1.062)	0.980 (0.875 to 1.097)	1.055 (0.859 to 1.295)
No history of diabetes	0.814 (0.760 to 0.872)	0.831 (0.752 to 0.917)	0.874 (0.726 to 1.052)
No history of hypertension	0.922 (0.786 to 1.081)	0.855 (0.674 to 1.085)	0.905 (0.594 to 1.381)
No history of chronic obstructive pulmonary disease	0.611 (0.566 to 0.660)	0.617 (0.553 to 0.689)	0.603 (0.489 to 0.744)
No history of coronary artery disease	0.601 (0.544 to 0.663)	0.688 (0.597 to 0.794)	0.669 (0.515 to 0.869)
No history of stroke	0.847 (0.795 to 0.902)	0.841 (0.766 to 0.922)	0.808 (0.683 to 0.955)
Sodium	0.959 (0.952 to 0.965)	0.950 (0.941 to 0.960)	0.959 (0.943 to 0.976)
Creatinine	1.015 (0.995 to 1.035)	1.006 (0.976 to 1.036)	1.051 (0.984 to 1.123)
Hemoglobin	0.924 (0.910 to 0.939)	0.922 (0.901 to 0.944)	0.938 (0.900 to 0.978)

BNP indicates B-type natriuretic peptide; CI, confidence interval.

Risk-Stratifying Patients for 30-Day HF Readmission

Our data may help clinicians utilize BNP when determining whether a patient hospitalized for HF is ready for discharge. BNP is a strong marker of HF severity and is correlated with other measures of elevated left ventricular filling pressures, such as pulmonary capillary wedge pressure²⁹ and tissue Doppler recordings.³⁰ Although several studies have reported results consistent with our findings, most were small or used a combined primary endpoint of either death and HF readmission,^{13,15–17,19,20,22,23,27,31,32} or death and all-cause readmission.^{12,14,18,21,26} In contrast, our study included over 50 000 patients and was thus powered to examine each outcome separately. In the present study, patients with a discharge BNP ≥ 1000 ng/L had a 30-day HF readmission rate of 15%, compared to only 4.1% for those whose discharge BNP was < 200 ng/L. Although admission BNP and percent change in BNP from admission to discharge were also associated with 30-day HF readmission, discharge BNP has several advantages. Not surprisingly, discharge BNP had the largest effect size when examining the association of BNP with 30-day HF readmission. Although our data indicate that admission BNP is measured in twice as many patients as discharge BNP, a BNP obtained at the time patients are deemed ready to leave the hospital may aid in discharge planning and will provide the

most accurate prognostic information. For example, a discharge BNP ≥ 1000 ng/L may cause clinicians to reconsider the timing of hospital discharge and/or arrange for earlier, more intensive outpatient follow-up. Discharge BNP values < 1000 ng/L, especially if decreased significantly from admission, may reinforce clinicians' impression when patients are otherwise deemed ready for discharge, with progressively lower values providing more reassurance. If widely implemented, this strategy may significantly reduce HF readmissions, because over 10 000 veterans were discharged with a BNP ≥ 1000 ng/L from 2006 to 2009.

The relation between BNP level and mortality is well documented in the literature.^{24,26,33–35} Consistent with previous studies, our data show a strong correlation between higher BNP values (admission and discharge) and smaller percent decreases in BNP from admission to discharge and 30-day mortality. The similarity between our mortality findings and those previously reported in the literature suggests that our findings regarding readmission and BNP may also be applicable to populations beyond the VA Health Care System.

HF Readmissions and Hospital Quality Metrics

We chose the primary endpoints of 30-day all-cause-, HF-, and non-HF-related readmission for several reasons. First, 30-day all-cause readmission rate after a hospitalization for HF is

Table 3. Discrimination and Net Reclassification for Readmission Models Using the 7187 Patients With Both Admission and Discharge BNP

	C-Statistic	P Value	Net Reclassification Improvement (NRI) (%)	P Value
30-day heart failure readmission				
Base clinical model	0.639	Reference		Reference
Base clinical model+discharge BNP	0.664	<0.0001	9.0	<0.0001
Base clinical model+admission BNP	0.649	0.14	2.7	0.07
Base clinical model+change in BNP	0.662	<0.0001	7.9	<0.0001
30-day all-cause readmission				
Base clinical model	0.625	Reference		Reference
Base clinical model+discharge BNP	0.634	0.002	5.4	<0.0001
Base clinical model+admission BNP	0.628	0.07	3.4	0.004
Base clinical model+change in BNP	0.631	0.03	4.3	0.0003
30-day readmission for other causes				
Base clinical model	0.596	Reference		Reference
Base clinical model+discharge BNP	0.601	0.23	2.6	0.15
Base clinical model+admission BNP	0.600	0.13	1.0	0.17
Base clinical model+change in BNP	0.603	0.14	2.6	0.13

BNP indicates B-type natriuretic peptide.

a widely used, publicly reported metric designed to judge the effectiveness of inpatient HF care provided by any Medicare-certified hospital (<http://www.hospitalcompare.hhs.gov>). Second, it is well known that HF hospitalizations account for a significant proportion of health care expenditures in the United States, costing an estimated \$20 billion annually.³⁶ Third, Medicare is penalizing hospitals with high readmission rates and is moving toward bundled episode payments as a method of decreasing health care costs.^{37,38} Despite these pressures, efforts to identify predictors of readmission in the HF population, such as patient demographics, comorbidities, hemodynamics, or laboratory values, have only been moderately successful.^{1,2,5-7} This is likely because the causes for hospital readmission in HF patients are heterogeneous, making them difficult to characterize and prevent. Our data indicate that BNP may aid in not only predicting readmission, but also in predicting certain types of readmission. Thus, high BNP levels during index admission have the potential to identify patients who may be particularly responsive to tailored therapy, such as delayed discharge (eg, ongoing intravenous diuresis) or high-intensity transitional care measures that specifically target HF pathology (eg, telemonitoring of weight changes).

Limitations

Although this is a large, national study, it has several limitations that should be taken into account when interpret-

ing the results. First, our population was mostly male, which limits the application of our findings to women. Additionally, we did not have measurements of height and weight, which may have improved the predictive value of BNP given its inverse association with adiposity.³⁹ Lack of echocardiography data precluded discrimination between HF patients with preserved ejection fraction and those with reduced ejection fraction; however, recent data suggest that BNP is associated with mortality and hospitalization even in patients with preserved ejection fraction.⁴⁰ Discharge medications and a measure of functional status were also not available; therefore, we could not adjust for evidence-based medical therapy use or NYHA functional class. Similarly, we could not adjust for HF etiology because angiography data were not available. Our data were limited to rehospitalizations paid for by the VA Health Care System; although this includes some non-VA hospitalizations, the true all-cause readmission rate is likely higher than reported. Finally, a relatively small proportion of patients had both an admission and discharge BNP measured during a hospital stay of greater than 2 days, which limited the analysis of percent change in BNP from admission to discharge.

Conclusion

In this study of over 50 000 veterans hospitalized with a primary diagnosis of HF, BNP levels measured during hospitalization were associated with 30-day HF readmission,

but not readmission for other causes. Specifically, patients with a discharge BNP ≥ 1000 ng/L had an unadjusted 30-day HF-specific readmission rate over 3 times as high as patients' whose discharge BNP was ≤ 200 ng/L (15% vs. 4.1%, respectively). These data may help clinicians identify patients at risk for HF-specific readmission, allowing disease management and transitional care interventions to be targeted to the highest risk population.

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Disclosures

None.

References

- Hernandez AF, Greiner MA, Fonarow GC, Hammill BG, Heidenreich PA, Yancy CW, Peterson ED, Curtis LH. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA*. 2010;303:1716–1722.
- Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418–1428.
- Allen LA, Tomic KES, Smith DM, Wilson KL, Agodoa I. Rates and predictors of 30-day readmission among commercially insured and Medicaid-enrolled patients hospitalized with systolic heart failure. *Circ Heart Fail*. 2012;5:672–679.
- Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA*. 2013;309:355–363.
- Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, Krumholz HM. Statistical models and patient predictors of readmission for heart failure: a systematic review. *Arch Intern Med*. 2008;168:1371–1386.
- Zaya M, Phan A, Schwarz ER. Predictors of re-hospitalization in patients with chronic heart failure. *World J Cardiol*. 2012;4:23–30.
- Hernandez MB, Schwartz RS, Asher CR, Navas EV, Totfalusi V, Buitrago I, Lahoti A, Novaro GM. Predictors of 30-day readmission in patients hospitalized with decompensated heart failure. *Clin Cardiol*. 2013;36:542–547.
- Kim H-N, Januzzi JL. Natriuretic peptide testing in heart failure. *Circulation*. 2011;123:2015–2019.
- Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647–654.
- Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161–167.
- Maisel A, Hollander JE, Guss D, McCullough P, Nowak R, Green G, Saltzberg M, Ellison SR, Bhalla MA, Bhalla V, Clopton P, Jesse R; Rapid Emergency Department Heart Failure Outpatient Trial Investigators. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol*. 2004;44:1328–1333.
- Michtalik HJ, Yeh H-C, Campbell CY, Haq N, Park H, Clarke W, Brotman DJ. Acute changes in N-terminal pro-B-type natriuretic peptide during hospitalization and risk of readmission and mortality in patients with heart failure. *Am J Cardiol*. 2011;107:1191–1195.
- Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E, Solal AC. Pre-discharge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol*. 2004;43:635–641.
- Faggiano P, Valle R, Aspromonte N, D'Aloia A, di Tano G, Barro S, Giovinozzo P, Milani L, Lorusso R, Dei Cas L. How often we need to measure brain natriuretic peptide (BNP) blood levels in patients admitted to the hospital for acute severe heart failure? Role of serial measurements to improve short-term prognostic stratification. *Int J Cardiol*. 2010;140:88–94.
- Valle R, Aspromonte N, Giovinozzo P, Carbonieri E, Chiato M, di Tano G, Feola M, Milli M, Fontebasso A, Barro S, Bardellotto S, Milani L. B-type natriuretic peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. *J Card Fail*. 2008;14:219–224.
- Valle R, Prevaldi C, D'Eri A, Fontebasso A, Giovinozzo P, Noventa F, Barro S, Carbonieri E, Milani L, Aspromonte N. B-type natriuretic peptide predicts postdischarge prognosis in elderly patients admitted due to cardiogenic pulmonary edema. *Am J Geriatr Cardiol*. 2006;15:202–207.
- Feola M, Aspromonte N, Canali C, Ceci V, Giovinozzo P, Milani L, Quarta G, Ricci R, Scardovi AB, Uslenghi E, Valle R. Prognostic value of plasma brain natriuretic peptide, urea nitrogen, and creatinine in outpatients >70 years of age with heart failure. *AJC*. 2005;96:705–709.
- Pimenta J, Paulo C, Mascarenhas J, Gomes A, Azevedo A, Rocha-Gonçalves F, Bettencourt P. BNP at discharge in acute heart failure patients: is it all about volume? A study using impedance cardiography to assess fluid and hemodynamic status. *Int J Cardiol*. 2010;145:209–214.
- Dhaliwal AS, Deswal A, Pritchett A, Aguilar D, Kar B, Soucek J, Bozkurt B. Reduction in BNP levels with treatment of decompensated heart failure and future clinical events. *J Card Fail*. 2009;15:293–299.
- Cournot M, Leprince P, Destrac S, Ferrières J. Usefulness of in-hospital change in B-type natriuretic peptide levels in predicting long-term outcome in elderly patients admitted for decompensated heart failure. *Am J Geriatr Cardiol*. 2007;16:8–14.
- Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;110:2168–2174.
- Di Somma S, Magrini L, Pittoni V, Marino R, Mastrantuono A, Ferri E, Ballarino P, Semplicini A, Bertazzoni G, Carpinteri G, Mulè P, Pazzaglia M, Shah K, Maisel A, Clopton P. In-hospital percentage BNP reduction is highly predictive for adverse events in patients admitted for acute heart failure: the Italian RED Study. *Crit Care*. 2010;14:R116.
- Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol*. 2001;37:386–391.
- Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:1943–1950.
- Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, Tognoni G, Cohn JN; Val-HeFT Investigators. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). *J Am Coll Cardiol*. 2008;52:997–1003.
- Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM, Hernandez AF. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes. *Circ Heart Fail*. 2011;4:628–636.
- Savarese G, Musella F, D'Amore C, Vasello E, Losco T, Gambardella F, Cecere M, Petraglia L, Pagano G, Fimiani L, Rengo G, Leosco D, Trimarco B, Perrone-Filardi P. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure. *JACC Heart Fail*. 2014;2:148–158.
- Cook NR, Ridker PM. The use and magnitude of reclassification measures for individual predictors of global cardiovascular risk. *Ann Intern Med*. 2009;150:795–802.
- Dokainish H, Zoghbi WA, Lakkis NM, Al-Bakshy F, Dhir M, Quinones MA, Nagueh SF. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. *Circulation*. 2004;109:2432–2439.
- Mak GS, DeMaria A, Clopton P, Maisel AS. Utility of B-natriuretic peptide in the evaluation of left ventricular diastolic function: comparison with tissue Doppler imaging recordings. *Am Heart J*. 2004;148:895–902.
- Valle R, Aspromonte N, Feola M, Milli M, Canali C, Giovinozzo P, Carbonieri E, Ceci V, Cerisano S, Barro S, Milani L. B-type natriuretic peptide can predict the

- medium-term risk in patients with acute heart failure and preserved systolic function. *J Card Fail.* 2005;11:498–503.
32. Valle R, Aspromonte N, Carbonieri E, D'Eri A, Feola M, Giovinazzo P, Noventa F, Prevaldi C, Barro S, Milani L. Fall in readmission rate for heart failure after implementation of B-type natriuretic peptide testing for discharge decision: a retrospective study. *Int J Cardiol.* 2008;126:400–406.
 33. Noveanu M, Breidthardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, Socrates T, Arenja N, Reiter M, Meissner J, Heinisch C, Stalder S, Mueller C. Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. *Crit Care.* 2011;15:R1.
 34. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. *J Am Coll Cardiol.* 2009;53:2343–2348.
 35. Luchner A, Möckel M, Spanuth E, Möcks J, Peetz D, Baum H, Spes C, Wrede CE, Vollert J, Müller R, Katus H, Giannitsis E. N-terminal pro brain natriuretic peptide in the management of patients in the medical emergency department (PROMPT): correlation with disease severity, utilization of hospital resources, and prognosis in a large, prospective, randomized multicentre trial. *Eur J Heart Fail.* 2012;14:259–267.
 36. Norton C, Georgiopoulou VV, Kalogeropoulos AP, Butler J. Epidemiology and cost of advanced heart failure. *Prog Cardiovasc Dis.* 2011;54:78–85.
 37. Mechanic R, Tompkins C. Lessons learned preparing for Medicare bundled payments. *N Engl J Med.* 2012;367:1873–1875.
 38. Cutler DM, Ghosh K. The potential for cost savings through bundled episode payments. *N Engl J Med.* 2012;366:1075–1077.
 39. Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Maisel AS. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *Am Heart J.* 2006;151:999–1005.
 40. van Veldhuisen DJ, Linssen GCM, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JGP, Paulus WJ, Voors AA, Hillege HL. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol.* 2013;61:1498–1506.