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Galectin 3 complements BNP in risk stratification in acute heart failure

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Abstract

Background—Galectin 3 (G3) is a mediator of fibrosis and remodeling in heart failure.

Methods—Patients diagnosed with and treated for Acute Heart Failure Syndromes were prospectively enrolled in the Decision Making in Acute Decompensated Heart Failure multicenter trial.

Results—Patients with a higher G3 had a history of renal disease, a lower heart rate and acute kidney injury. They also tended to have a history of HF and 30-day adverse events compared with B-type natriuretic peptide.

Conclusion—In Acute Heart Failure Syndromes, G3 levels do not provide prognostic value, but when used complementary to B-type natriuretic peptide, G3 is associated with renal dysfunction and may predict 30-day events.

Keywords

acute heart failure; renal disease; risk stratification

Introduction

Acute heart failure syndromes (AHFS) comprise the primary admitting diagnoses for over one million patients per year in the United States. Hospitalization for AHFS has tripled in the last three decades, and AHFS is the top reason for admitting patients over 65 years of age to the hospital (Ahmed et al. 2008, Rosamond et al. 2008). In AHFS patients with

similar probability of death at presentation, those treated and released from the Emergency Department (ED) may have higher 90-day mortality than those admitted to the hospital for treatment (Lee et al. 2010). The Lee et al study suggests that the decision of whether to admit the AHFS patient for treatment or whether to initiate treatment in the ED with the goal of achieving early discharge home has measurable implications for patient outcomes.

Natriuretic peptides, in particular B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP), are increasingly being used to guide the management of AHFS patients. (Dickstein et al. 2008) However, BNP and NT-proBNP values are very much influenced by many factors including age, renal function, and anemia (Hogenhuis et al. 2007). In addition, there is a relatively large range of values for BNP over which it provides little support to decision making in patients who present with undifferentiated dyspnea (Brenden et al. 2006). As a result, there is a clear need for complementary biomarkers that would provide additional information to assist in ED diagnosis and short term prognosis in patients with AHFS.

Galectin-3 (G3) is a soluble beta galactoside binding-lectin secreted by activated macrophages that interact with several extracellular matrix components (Ochieng et al. 2004). In healthy hearts, G3 expression is low but its expression increases in hypertrophy leading to heart failure (Sharma et al. 2004). G3 has long-term prognostic value in patients with stable advanced heart failure (Lok et al. 2010, de Boer et al. 2011a, Tang et al. 2011, de Boer et al. 2011b, Lopez-Andres et al. 2012). Recent evidence suggests serum G3 measurements are not only elevated in patients with stable heart failure, but may also be predictive of adverse outcomes in AHFS (van Kimmenade et al. 2006).

While G3 shows promise in detecting long-term outcomes, the role of admission G3 levels in early risk stratification in patients with AHFS is undefined. In addition, the ability of G3 to complement the information provided by BNP has only recently been explored (Shah et al. 2010, Grandin et al. 2012, Felker et al. 2012). The hypothesis of this investigation is that elevated admission G3 levels would be associated with increased risk for 5- and 30-day AHFS-related events in ED patients with AHFS. Further, we hypothesize that elevated G3 provides additional risk stratification information when compared with BNP alone.

Methods

Study population

This was an Institutional Review Board approved nested cohort study that included patients from the Decision Making in Acute Decompensated Heart Failure (DECIDE) study. DECIDE is an ongoing prospective cohort study of adults presenting to one of five emergency departments with signs and symptoms of AHFS. The DECIDE study was designed to explore risk stratification after initial therapy in heart failure patients presenting to the ED, and was approved by the Institutional Review Boards of participating sites. Potential participants were recruited by clinical study assistants. Patients with dyspnea, cough, and/or acute pulmonary edema on chest radiography were screened for inclusion. Patients that met physician-assessed modified Framingham criteria (Table 1) were treated for AHFS with either vasodilators or diuretics, and who could be enrolled within three hours of first physician contact and within one hour of treatment were enrolled. To be included in this nested cohort, participants must have been enrolled at three of the five sites and have blood specimens available for analysis. Patients screened, enrolled, followed up and included in this cohort are described in Figure 1.

Data collection

After participants provided written, informed consent, clinical study assistants collected socio-demographic and medical history data direct from the patients, supplemented with information from the medical records. Baseline clinical data, including physical exam findings, vital signs, laboratory and imaging data and treatments, were collected from the medical record. Additional clinical data were obtained at 12–24 hours and 72–96 hours after ED treatment. At baseline, 12–24 hours and 72–96 hours, any laboratory testing not performed for clinical purposes was conducted for research purposes, and blood samples were obtained and banked for future study. The blood samples were centrifuged at $2000 \times g$ for 10 min at room temperature; the plasma was divided into 1 mL aliquots, and stored at -80°C . Clinical study assistants performed follow-up patient interviews at both 5 and 30 days after enrollment to document adverse events. Follow-up was in person for patients in the hospital, and by telephone for patients who had been discharged. Follow-up data were supplemented with information obtained direct from the medical record. Adverse events included unscheduled ED visits for HF, unscheduled hospital admissions for HF, and death from any cause.

G3 assay

Plasma G3 levels were determined using an FDA cleared enzyme-linked immunosorbent assay kit (Galectin-3 Assay™, BG Medicine, Waltham, MA, USA) and were measured on a Bio-tekELx800 microplate reader (Biotek Instruments, Winooski, VT, USA). Calibration of the assay was performed according to the manufacturer's recommendations and values were normalized to a standard curve. The characteristics of this assay are previously described (Christenson et al. 2010).

Statistical analysis

All analyses were conducted using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are described using median and range, or frequency and percent, as appropriate. BNP for three patients were missing BNP; missing values for BNP were imputed using multiple imputation. To determine whether or not G3 was associated with risk for adverse events, initial analysis used logistic regression to determine the increase in probability of events for each decile increase in G3. A cut-point was then selected at which the risk for an adverse event began to increase; this occurred between the 7th and 8th decile so patients were stratified into two groups with those with a G3 in the upper quartile were compared to the remainder. Confidence intervals were calculated for differences in medians or proportions.

With a high colinearity between G3 and BNP, it is not straightforward to determine whether they provide complementary information in the risk stratification of patients with AHFS. *A priori*, we planned to explore the residuals from the regression of G3 on BNP as a predictor of adverse events. If G3 is assumed to provide no complementary risk information to BNP, then there would be no association between the residuals and risk of adverse events. Any association between the residual and the risk of adverse events would suggest that if G3 were larger or smaller than might be expected from the level of BNP, it is providing complementary information that impacts the estimate of a patient's risk.

Results

Baseline characteristics

There were 203 patients with G3 values; two were lost to follow-up at 5 days and were excluded. Median age of the 201 included subjects was 66 years (range 27–99 years), 71(35.3%) were African-American and 118 (58.7%) were male. The cohort included 155

(77.1%) patients with a history of heart failure and 55 (27.4%) patients with a history of renal disease. Patients are described in Table 2.

Association with clinical characteristics

Patients with G3 levels in the upper quartile (29.9 ng/ml–82.7 ng/ml) were more likely to have a history of heart failure (88% vs. 74%, difference 14%, 95% CI 1 to 24) and were more likely to have a history of renal disease (56% vs. 18%, difference 38%, 95% CI 23 to 52) than all other patients. Similarly, patients with G3 levels in the upper quartile had a higher median BNP (1190 pg/ml vs. 731 pg/ml, difference in medians 459 pg/ml, 95% CI 68 to 987), higher median creatinine (2.4 mg/dl vs. 1.2 mg/dl, difference in medians 1.2 mg/dl, 95% CI 0.6 to 1.8) and higher median BUN (35 mg/dl vs. 17 mg/dl, difference in medians 18 mg/dl, 95% CI 9 to 27) (Table 3). Other clinical characteristics did not differ between groups.

Association of G3 levels with outcomes

Median G3 values were similar between those with and without 30-day events (25 ng/ml vs. 22 ng/ml, difference in medians 3 ng/ml, 95% CI 3 to 9, respectively). However, subjects with a G3 value in the upper quartile were more likely to have 30-day events than those with lower G3 levels (28% vs. 15 %, difference 13%, 95% CI 1 to 28).

Association between G3, BNP, and outcomes

Figure 2 shows the scatterplot of G3 against BNP. It is clear there are cases with a higher G3 than would be expected from their BNP, and cases with a lower G3 than would be expected. Table 4 describes those with a concordant BNP and G3, those with a higher G3 than would be expected and those with a lower G3. Patients with a higher G3 than would be expected based on their BNP were more often Caucasian, had a history of renal disease, a lower heart rate and more severe acute renal dysfunction compared to those with concordant or lower G3 than would be expected. There were also trends toward higher than expected G3 values in those with a history of HF and those with 30-day adverse events.

Discussion

Our data suggest that G3 provides additional and complementary risk information compared with BNP alone. A patient with a G3 level that is higher than would be predicted by their BNP level were more likely to have a history of renal disease, a lower heart rate, and more severe acute renal dysfunction. Although not statistically significant these patients also tended to have more 30-day adverse events and history of heart failure. Independent of BNP, high G3 levels were also associated with higher 30-day adverse event rates.

Pathobiology of G3 and BNP

G3 is a protein released by activated macrophages that stimulates fibroblast proliferation and collagen synthesis. G3 is found in the early phases of maladaptive responses that herald the progression to heart failure. It has been shown to be elevated in dyspneic patients with echocardiographic markers of valvular regurgitation, impaired LV filling, and RV dysfunction (Shah et al. 2010). Conversely, BNP is peptide neurohormone released by ventricular myocytes primarily in response to myocardial stretch. Given the distinct pathobiology, there is reason to believe that G3 might provide different information to BNP.

Risk stratification markers in HF

Studies designed to develop tools for risk stratifying patients with AHFS during an acute presentation, such as the DECIDE study; typically use statistical models to estimate

individual risk. They incorporate variables such as physiologic parameters, ECG, renal function, electrolytes, myocardial necrosis markers and based upon their extreme association with AHFS status, natriuretic peptides. Since the natriuretic peptides are so strongly associated with an AHFS presentation and subsequent outcomes, a consideration for evaluating new candidate markers is what additional utility they may have. Such considerations must include whether they assess a different physiological phenomenon, and whether that phenomenon is likely associated with diagnostic and prognostic outcomes that are not already captured by existing markers.

Long-term risk stratification

The majority of research with G3 has focused on longer term outcomes. As such, G3 was cleared by the US Food and Drug Administration for the prognostic assessment of patients with chronic HF. In a subgroup of severe, chronic HF in the Deventer-Alkmaar Heart Failure Study (DEAL-HF) baseline G3 was a predictor of long-term mortality (6.5 years) after correction for age, sex, chronic kidney disease and NT pro BNP (Lok et al. 2010). In a European cohort of 168 patients with chronic NYHA class II-IV HF, baseline G3 levels were correlated to long-term all-cause mortality for a 2.9 year follow-up period (Ueland et al. 2011). Finally, in a substudy of the Cardiac Resynchronization in Heart Failure Trial (CARE-HF), investigators found an age and gender adjusted association of elevated G3 levels and cardiovascular death and HF rehospitalization in their 18 month study period (Lopez-Andres et al. 2012). Given the weight of evidence, using G3 as an extracellular matrix marker (ECM) for pathological remodeling and subsequent long-term (greater than 12 months) morbidity and mortality appear to be well supported.

Short, midterm risk stratification

Since prior clinical investigations of G3 have focused on longer term outcomes, our current study uses patient data from an ongoing study to test the candidate marker in 5- and 30-day time frames. Search for comparator studies of shorter term stratification finds only two prior investigations. Using data from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study, investigators examined G3 levels in patients with AHFS. Elevated admission G3 was found to be the best independent predictor of 60-day mortality (OR 10.3, $p < 0.01$) or the combination of death/recurrent HF within 60 days (OR 14.3, $p < 0.001$). Kaplan Meier analysis revealed that the combination of G3 and NT pro-BNP predicts 60-day mortality better than either marker in isolation. (van Kimmenade et al. 2006)

The clinical scenario of the development of new or worsening HF subsequent to an acute coronary syndrome (ACS) presentation is of import to Emergency Physicians and was investigated using pilot data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) cohort (Grandin et al. 2012). G3 was measured at baseline, defined as within 7 days post ACS. Patients who developed HF had higher baseline G3 levels [median 16.7 $\mu\text{g/L}$ (25th, 75th percentile 14.0, 20.6) vs. 14.6 $\mu\text{g/L}$ (12.0, 17.6), $p = 0.004$]. Patients with baseline G3 above the median had an odds ratio of 2.1 (95% CI 1.2–3.6) for developing HF, ($p = 0.010$). After adjusting for prior HF, prior MI, hypertension and diabetes, baseline G3 elevations continued to show a graded association across all quartiles for the development of HF (OR 1.4). The association G3 and development of HF was attenuated, but remained significant, when BNP was introduced into the model (OR 1.3). While this trial broadens the potential role for G3 as a prognostic biomarker in patients with established HF to those with acute ischemic heart disease at risk for future HF, the undifferentiated time frame of the risk stratification (0–24 months) is insufficient to impact the emergency care of this HF subpopulation.

Our investigation adds to the current body of literature in that it uniquely examines risk stratification in a time-frame of interest to acute cardiac care. Since rat model experimental evidence suggests that the expression of G3 is modifiable, some authors advocate for its potential as a therapeutic target (Liu et al. 2009). More practically, the adverse event signal at 30 days may, for example, drive changes triage decisions to higher acuity inpatient settings. In addition, a higher 30-day adverse event rate may drive clinicians to deploy advanced diagnostics and therapeutics, such as implantable monitoring devices and cardiac resynchronization therapy. Health systems may find more attentive posthospitalization follow-up with outpatient home visits are indicated in the subpopulation with a higher 30-day event rate.

Association with renal dysfunction (acute and/or chronic)

We note that G3 has an association with renal injury, supported in our study by the association between G3 and creatinine. Renal injury is defined in this investigation as an elevated serum creatinine and cannot be further characterized and acute, chronic or both. Renal injury is associated with poor short term heart failure outcomes (Fonarow et al. 2008); and so we hypothesize that future investigation may reveal an association between elevated G3 and short term outcomes mediated by renal injury. Arterial noncompliance and renal insufficiency have strong associations (Shah et al. 2010). G3 is a key feature of fibroblast activation in a murine renal fibrosis model, (Henderson et al. 2008) which is a mechanism similar to cardiac fibrosis. The murine model found macrophage secretion of G3, rather than tubular reabsorption of G3, to be a central feature in renal fibrosis. Since the pathophysiology of both cardiac and renal failure appears to be interrelated, G3 may be reflective of the collagen burden in both organs. While G3 may be reflective of direct cardiac injury, increased morbidity and mortality associated with elevated G3 levels could be a marker of direct renal injury. Perhaps G3 may prove to have a stronger association with renal dysfunction and thus be a marker of renal failure in the heart failure population. The association found with serum creatinine in this investigation provides evidence supporting the importance of the cardiorenal syndrome.

HF phenotypes

Our cohort included diverse heart failure phenotypes; those with heart failure with preserved ejection fraction (HFPEF) and heart failure with reduced ejection fraction (HFREF). The baseline characteristics of this cohort are similar to other large population-based AHFS registries and reflect the spectrum of comorbidities and event rates typically seen in clinical practice (Januzzi et al., 2005, Fonarow et al., 2008) Several of the early studies describing the role of G3 in the long-term risk stratification of HF enrolled patients with HFREF by using LVEF as an inclusion criteria. However de Boer et al., found a stronger association of elevated G3 and mortality in patients with HFPEF over those with HFREF (de Boer et al., 2011a). In a cohort of 592 patients hospitalized for heart failure, a doubling of G3 levels was an independent predictor of primary endpoints of all-cause mortality and heart failure rehospitalization over the 18 month study period. There is also some evidence that patients with pulmonary hypertension and right ventricular dysfunction exhibit G3 elevations. Subgroup analysis using echocardiographic parameters has suggested that fibrosis and remodeling of the right ventricle is similar to that observed in the left ventricle. (Shah et al., 2010)

Incremental value over BNP

The ability of G3 to provide incremental prognostic value over traditional pressure-dependent biomarkers, such as the natriuretic peptides has been the subject of secondary analysis in many of the studies already cited. de Boer *et al* found after correcting for age, gender, BNP, eGFR, and diabetes the HR was 1.38 (1.07–1.78; $p = 0.015$) for G3 alone in

the prediction of the primary endpoint of all-cause mortality and HF rehospitalization. Combining G3 and BNP increased prognostic value over either biomarker alone (ROC analysis, $p < 0.05$) (de Boer et al. 2011a). Using the PRIDE AHFS cohort, van Kimmenade et al., reported that ROC analysis for mortality prediction at 60-day, and combined death/HF readmission at 60 days G3 had the greatest area under the curve (AUC) at 0.74 ($p = 0.0001$), whereas NT-proBNP had an AUC of 0.67 ($p = 0.009$). The addition of NT-proBNP seemed to refine the predictive utility at 60 days for the combined end-point (van Kimmenade et al. 2006). Conversely, Grandin reported that addition of a natriuretic peptide attenuates the predictive value of G3 for the outcome of new or worsening HF within 18 months after an ACS event (Grandin et al. 2012). The findings depicted in Figure 2 suggest that there may be a nonlinear component to the G3 values that are discordant with BNP. Perhaps at very high and very low BNP levels G3 may add more prognostic value. While both marker classes appear to offer some prognostic utility, further study is warranted to determine their relative contributions.

In summary, this investigation reveals that there is some association between G3 and 30-day outcomes in patients with AHFS, but no association with shorter term outcomes. We found a subset of patients, whose G3 levels were elevated beyond what would be predicted by their BNP elevations, and these patients were more likely to have acute kidney injury, and there was a tendency towards an increased 30-day event rate. Since these associations were based on discordance between BNP and G3, it is possible that G3 could be useful for identifying the subset of patients with cardiorenal syndrome that is not identified as high-risk when natriuretic peptides are used in isolation. Further study should consider how a multimarker approach can help the physician differentiate AHFS phenotypes and provide risk stratification information specific to different pathways of disease progression. Indeed, such an approach might prove useful in guiding treatment strategies.

Limitations

While this secondary analysis suggests G3 is associated with renal dysfunction and 30-day events and may provide complementary information to BNP, some limitations exist. This investigation had a modest sample size and very few 5-day events. A larger cohort would allow for increased scrutiny of short term outcomes. While G3 levels in the top quartile were associated with elevations in BNP, BUN and creatinine, further investigation should explore those AHFS patients with adverse events and elevated G3 level but with normal levels of BUN, creatinine and BNP. Finally, patients were enrolled based on ED diagnosis and treatment for AHFS. While this is highly representative of clinical practice, bias may have been introduced in those patients where the ED physician incorrectly diagnosed AHFS. The ED diagnosis disagrees with a cardiology chart review in approximately 15% of cases (McCullough et al. 2002, Doust et al. 2004).

Conclusion

Patients with AHFS whose G3 levels are higher than would be predicted by their BNP levels were more likely to have a history of renal disease, a lower heart rate, and more severe renal dysfunction. These patients also tended towards more 30-day adverse events. Further study to explore how complementary biomarkers improve the differentiation between AHFS phenotypes and facilitate prognosis and treatment decisions is warranted.

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Declaration of interest

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Figure 1.
Patient enrollment and flow through the study.

Figure 2.

Scatterplot of galectin 3 against B-type natriuretic peptide with the regression line shown. Cases are shaded according to the magnitude of the residuals. Those with a residual in the top quartile have a higher than expected galectin 3, those in the bottom quartile have a lower than expected galectin 3.

Table 1

Modified Framingham criteria.

Major	Minor
History of heart failure	Extremity edema
Paroxysmal nocturnal dyspnea	Night cough
Pulmonary or interstitial edema (on CXR)	Dyspnea on exertion
	Hepatomegaly
Rales	Pleural effusion
Cardiomegaly	Tachycardia (> 130 beats/min)
S ₃ gallop	
Jugular venous distention	
Positive hepatojugular reflux	

* Two major or one major and two minor criteria are required to establish a preliminary diagnosis of heart failure by the Framingham criteria. CXR, chest x-ray.

Table 2

Demographics: data are presented in median and range or frequency and percent.

Age (year)	66	27–99
African–American	71	35.3%
Male	118	58.7%
History of heart failure	155	77.1%
History of renal disease	55	27.4%
Heart rate (/min)	85	49–65
Respiratory rate (/min)	20	12–90
Systolic BP (mmHg)	143	89–262
BNP (pg/ml)	772.0	9.0–5050.6
BUN (mg/dl)	21	4–105
Sodium (mEq/L)	139	100–147
Creatinine (mg/dl)	1.3	0.5–9.6
Five day event	3	1.5%
Thirty day event	36	17.9%

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen.

Table 3

Association of galectin 3 with clinical characteristics and laboratory results.

	</= 75 th percentile ^a	>75 th percentile ^b	Difference	95% CI		p value		
				Lower	Upper			
Age	66	27-99	67	31-94	-1.0	-5.1	7.1	0.856
African-American	59	39.1%	12	24.0%	15.1%	-0.3	27.6	0.053
Male	88	58.3%	30	60.0%	1.7%	-14.0	16.5	0.83
History of heart failure	111	73.5%	44	88.0%	14.5%	1.1	24.4	0.024
History of renal disease	27	17.9%	28	56.0%	38.1%	22.8	52.0	<0.001
Heart rate	85	49-165	86	50-140	0.5	-5.3	6.3	0.533
Respiratory rate	20	12-90	20	12-32	0.0	1.8	-1.8	0.946
Systolic BP	147	89-262	139	96-221	-8.5	-19.2	2.2	0.043
BNP	731.0	9.0-4850.0	1190.5	26.0-5050.0	459.5	-68.3	987.3	0.025
BUN	17.0	4.0-83.0	35.0	10.0-105.0	18.0	8.7	27.3	<0.001
Sodium	139.0	100.0-146.0	138.0	128.0-147.0	-1.0	-2.0	0.0	0.135
Creatinine	1.2	0.5-6.8	2.4	0.9-9.6	1.2	0.6	1.8	<0.001
Five day event	3	2.0%	0	0.0%	-2.0%	-5.3	5.7	0.422
Thirty day event	22	14.6%	14	28.0%	13.4%	1.1	27.9	0.032

^a 7.3-29.7 ng/ml.^b 29.9-82.9 ng/ml.

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen.

Table 4

Patient characteristics by level of BNP and galectin 3 discordance. Data are given in median and range or frequency and percentage.

	Values less than expected ^a		Values as expected ^b	Values more than expected ^c		p value	
Age	61	27–99	68	32–91	70	31–94	0.161
Race							
Caucasian	24	47.1%	66	66.7%	40	78.4%	0.003
African-American	27	52.9%	33	33.3%	11	21.6%	
Sex							
Male	29	56.9%	62	62.6%	27	52.9%	0.497
Female	22	43.1%	37	37.4%	24	47.1%	
Heart failure							
No	15	29.4%	25	25.3%	6	11.8%	0.077
Yes	36	70.6%	74	74.7%	45	88.2%	
Renal disease							
No	48	94.1%	72	72.7%	26	51.0%	p<0.001
Yes	3	5.9%	27	27.3%	25	49.0%	
Heart rate	93	51–165	84	49–134	79	50–140	0.004
Respiratory rate	20	12–90	20	14–80	20	12–32	0.400
Systolic BP	150	92–224	143	89–262	139	96–207	0.127
BNP	1197.0	206.0–4850.0	627.0	9.0–4462.0	832.0	26.0–5050.6	0.002
BUN	15.0	4.0–45.0	19.0	4.0–83.0	33.0	10.0–105.0	p<0.001
Sodium	140.0	130.0–145.0	139.0	100.0–146.0	138.0	128.0–147.0	0.195
Creatinine	1.1	0.6–2.5	1.3	0.5–6.8	1.9	0.9–9.6	p<0.001
Five day event							
No	49	96.1%	98	99.0%	51	100.0%	0.226
Yes	2	3.9%	1	1.0%	0	0.0%	
Thirty day event							
No	42	82.4%	86	86.9%	37	72.5%	0.095
Yes	9	17.6%	13	13.1%	14	27.5%	

^aDifference in predicted and actual G3 –25.98 to –7.35.

^bDifference in predicted and actual G3 –7.36 to –1.85.

^c Difference in predicted and actual G3 -1.86 to 39.20 .

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen.