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Association of BNP and Troponin Levels with Outcome among Cardiac Resynchronization Therapy Recipients

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Abstract

Introduction—We conducted a prospective multicenter study to assess the prognostic value of combined baseline pre-implant plasma levels of the biomarkers cardiac troponin T (TnT) and BNP among CRT-D recipients.

Methods—At CRT-D implant, patients were stratified based on detectable TnT (≥0.01 ng/ml) and elevated BNP (predefined as >440 pg/ml) levels. Patients were classified into 3 groups high (both detectable TnT and high BNP), intermediate (either detectable TnT or high BNP), or low (non-detectable TnT and low BNP). Patients were followed for 12 months. Survival curves free from mortality or HFH were assessed. To assess the predictive value of biomarker category, we constructed a multivariate Cox regression model, including the covariates of age, NYHA class, LVEF, and QRS duration.

Results—A total of 267 patients (age 66 ± 12 years, males 80%, LVEF 25% ± 8%, ischemic CM 52%, QRSd 155 ± 26 ms) were studied. After one year, there were 13 deaths and 25 HFH events. A significant difference in event free survival among the 3 groups was observed, with high and

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intermediate categories having worse survival than low (log-rank test, p <0.001). In the multivariate model, risk category was a significant predictor of outcome: Hazard ratios were 7.34 (95% CI: 2.48 to 21.69) and 2.50 (95% CI: 1.04 to 6.04) for high and intermediate risk groups respectively (p<0.0001).

Conclusion—Among CRT-D recipients, baseline TnT and BNP values alone or in combination provide significant prognostic value for the outcome of mortality or HFH.

Keywords

Biomarkers; BNP; Cardiac Resynchronization Therapy; Congestive Heart Failure; Troponin

Introduction

Among appropriate patients with advanced heart failure, cardiac resynchronization therapy (CRT) with or without defibrillator capability (CRT-D) has been shown to improve survival and decrease heart failure hospitalizations (HFH), in association with reverse remodeling of the left ventricle.[1,2] However, a persistent finding has been that a significant proportion of CRT recipients will not benefit from this therapy, so called non-responders. Recent evidence demonstrates greater benefit in applying CRT earlier in the course of the disease.[3–5] Biomarkers may help identify patients likely to benefit CRT and to monitor subsequent response among recipients. Two commonly used biomarkers may have a complimentary role in assessing the stage of cardiomyopathy and heart failure progression. B-type natriuretic peptide (BNP) is an endogenous peptide secreted by cardiac myocytes in response to stretch from pressure or volume overload the main function of which is to promote vasodilation and renal excretion of sodium and water.[6] BNP has been widely used as a marker of HF progression and a monitor for therapy.[7–9] Cardiac troponin T is a structural contractile protein specific to the myocardium that can be detected in trace amounts using modern assays. Circulating troponin subtypes have been associated with ischemic or non-ischemic cardiomyopathy with or without heart failure.[10–12] Systemic release of cardiac troponins including troponin subtype T (TnT) in such cases has been attributed to ongoing cardiac cell necrosis or leakage of soluble cytosolic components due to compromised cell membrane integrity. Among patients with cardiomyopathy, elevated levels of either biomarker, particularly in face of optimal therapy, have been associated with worse prognosis.[9–14] In combination, these biomarkers provide significant prognostic information, however, their value has not been explored among CRT-D recipients.[15,16]

We conducted a multicenter study; “RISK Stratification Using a Combination of Cardiac Troponin T and Brain Natriuretic Peptide in Patients Receiving CRT-D (RISK)” to assess whether the combined biomarkers BNP and TnT measured at baseline before CRT-D implant would be associated with subsequent heart failure outcome and overall response to therapy. We assessed the combined endpoint of HFH or death through one year after CRT-D implant. In secondary analysis, we examined the association of biomarker levels at baseline and on follow up with the primary outcome, CRT response and defibrillator shocks.

Methods

In this multicenter prospective observational study (RISK) we recruited adult patients with heart failure and stable optimal pharmacological therapy undergoing CRT-D implant as clinically indicated.

To qualify for CRT-D, patients met standard guideline directed indications at the time of enrollment and were on stable guideline directed medical therapy. For the purpose of the study, stable therapy for both beta-blockers and ACE-I/ARB was considered to be: Dose increases no more than 100% greater than initial dose at 30 days before study enrollment, or decreases in dosing < 50% of initial dose at 30 days before study enrollment with no changes in the 30 days preceding enrollment. Aldosterone blockers were encouraged but not mandated. Patients were excluded if they refused or withdrew consent, did not receive a transvenous CRT system, had recent (<30 days) acute ischemic syndrome or acute decompensation of heart failure.

At baseline visit, patients received a history and physical exam, responded to a standard heart failure quality of life questionnaire (Minnesota Living with Heart Failure Questionnaire: MWLHFQ), underwent a standard echocardiogram and 12 lead EKG, had a blood sample drawn for BNP and TnT and underwent a standard six minute hall walk test. Biomarker levels were repeated pre-discharge and at three monthly intervals until six months. At 12 months the same baseline investigations including echocardiograms were repeated.

A structured questionnaire for determination of NYHA class was provided to all sites. The reported NYHA class was therefore different than inclusion and was adjusted for in the multivariate analysis model. Echocardiograms at baseline pre-implant and at 12 months were acquired according to a pre-specified protocol and analyzed by a central core lab (University of Pittsburgh Medical Center, PA, USA).

The primary outcome measure was death or first HFH within the first year of follow up. For a hospitalization to qualify as HFH it needed to satisfy both of the following criteria: 1. Admission to hospital for >24 hours with one of the following HF worsening symptoms: Increased heart failure class, orthopnea, paroxysmal nocturnal dyspnea, edema, dyspnea on exertion, or gastrointestinal symptoms attributable to HF, and 2. Receipt of any of the following for heart failure within 24 hours of admission: Intravenous diuresis or intravenous inotropic medications. All admissions were blindly adjudicated by two members of the steering committee to have met these criteria.

Response to CRT was assessed as freedom from HFH or death and improvement in end systolic volume (ESV) by 15%. Device interrogations were performed at quarterly intervals and whenever clinically indicated. All shocks were independently adjudicated by blinded reviewers from the steering committee as appropriate or inappropriate according to standard criteria.

Biomarker Assessment

Blood samples, collected from a venous access after a resting time of 15 minutes, were drawn into pyrogen-free blood collection tubes with EDTA as anticoagulant, immediately immersed in ice, and centrifuged at 2,000g for 15 minutes within 30 minutes. All samples were stored at −80°C and shipped to a central core laboratory (Veterans Affairs San Diego Healthcare System, California, USA), until measurement of TnT, and BNP on a Modular platform ; Roche Elecsys 2010 (Roche Diagnostics, Indianapolis, IN) and Bayer Advia Centaur (Siemens Healthcare nee Bayer, Tarrytown, NY), resp. BNP was determined by Direct Chemiluminescence using Acridinium Ester technology (BNP, Siemens Healthcare). TnT was measured by electrochemiluminescence immunoassay (Elecsys Troponin T, Roche Diagnostics). TnT values below < 0.010 ug/L or ng/mL are reported as undetectable.

Data Analysis and Statistical Methods

Patients were divided into groups based on detectable TnT or elevated BNP. Cut points of 0.01ng/ml for TnT and 440 pg/ml BNP were predefined based on previously published studies of BNP[9,13,16,20] and TnT[10,15] in similar cohorts. Patients were divided into low risk group who had no detectable TnT and low BNP, intermediate risk with either detectable TnT or elevated BNP and high risk with both detectable TnT and elevated BNP. Based on the assumption of doubling risk between groups[13], a significance level of 0.0167 and power of 80%, 272 patients were estimated to be required.

Descriptive statistics of the baseline characteristics are presented as mean ± SD. Comparisons between groups were made using Chi square or Fischer exact tests for categorical variables while continuous variables were compared using Kruskal-Wallis one way analysis of variance. Survival curves free from mortality or HFH were assessed.

Regression models to estimate the strength of association between baseline variables and outcomes were constructed. To assess the independent predictive value of biomarker category, we constructed a multivariate Cox regression model. Baseline variables with associations approaching significance in addition to the predetermined covariates of age, gender, NYHA class, LVEF, and QRS duration were entered into stepwise multivariate regression models. Age, LVEF and QRS duration were included as continuous variables. Co-linearity between variables was assessed and multivariate models were adjusted accordingly. Stepwise selection of the variables was performed as follows: The most significant variable was picked, then, the most significant variable to meet the 5% level was picked among the remaining variables. Results of the Wald test for individual parameters were examined. The least significant variable that does not meet the 5% level for staying in the model was then removed. The stepwise selection process ended if no further variable could be added to the model or if the variable just entered into the model was the only variable removed in the subsequent backward elimination.

Results

Between 11/2005 and 5/2011, 267 patients were recruited at 32 participating centers (appendix) who successfully received a transvenous CRT-D device, had baseline biomarker

values and completed the required 12 month follow up in the study. Baseline variables for the cohort as whole and for risk groups are presented in Table I. Patients were mainly older males (age 66 ± 12 years, males 80%, LVEF 25% ± 8%, ischemic cardiomyopathy 52%, QRSd 155 ± 26 ms). While there was no difference among the groups in ejection fraction, ischemic etiology of cardiomyopathy or QRS duration, there were significant differences among the groups in renal function, utilization of beta blockers, score on the MLWHFQ and performance on the 6 min walk test at baseline.

The distribution of BNP levels among the cohort is shown in figure 1. The median BNP was 198pg/ml and the third quartile was at 438pg/ml; nearly identical to the predetermined cutpoint of 440pg/ml. There were a total of 64 patients with detectable TnT (44 in intermediate group and 20 in high risk group, Fig. 2). Most patients (59.2%) were in the low risk group while intermediate and high risk groups were a successively lower proportion (33.3% and 7.5% respectively). The intermediate group was equally divided between those with high BNP and detectable troponin I (50.4% and 49.6%, respectively). Figure 2 demonstrates the distribution of both biomarker levels among risk groups.

Baseline Risk Group and Primary Outcome

After one year follow up, there were 13 deaths and 24 HFH episodes for 19 unique patients. Of those, two patients subsequently died. Thus, among the cohort as a whole 30 unique patients met the primary outcome measure. The distribution of patients meeting the primary outcome among risk groups is shown in Table 2. Figure 3 demonstrates the KM survival curves for freedom from primary outcome among the three groups. The log rank statistic showed a significant difference among the survival curves (p=0.001). On univariate analysis, compared to the low risk group, being among the high risk group conferred an excess of 6 fold risk while being in the intermediate group more than doubled it (HR:6.2, CI: 2.29–16.83 and HR: 2.38, CI:1.07–5.32 for high and intermediate risk groups respectively, p =0.001). Other significant ($p<0.05$) univariate risk factors were found to include: QRS duration and ejection fraction. Variables included in the multivariate model in addition to risk group were age, NYHA, EF and QRS duration. Risk group was found to retain its independent prognostic value (HR 7.34, CI: 2.48–21.69, and HR 2.50, CI: 1.04–6.04 for high risk and intermediate risk groups compared to low risk group, respectively; P=0.001). In addition to risk group, age, QRS duration and ejection fraction remained in the final model (figure 4). Although baseline serum creatinine approached significance on univariate analysis it was highly co-linear with risk group and was not included in the final model based on methodology described above.

Change in Risk Group and Primary Outcome Measure

Change in biomarker risk group by 6 months was assessed for its potential value as a prognostic marker. Patients were assessed as having improved (21%), no change (69%) or worsened (10%) risk based on the risk group they fell into by 6 months compared to baseline. Worsened risk group was driven by detectable TnT (60%) or increase in BNP above cutpoint in (40%). Worsened risk group was negatively associated with the primary outcome on univariate analysis (HR: 0.2, CI: 0.05–0.8 and, HR: 0.12 CI: 0.04–0.37, $p < 0.001$) for improved versus worsened and no change versus worsened, respectively. On

multivariate analysis the negative association with worsened risk group remained significant (HR: 0.22, CI: 0.05–0.64 and HR: 0.13, CI: 0.04–0.42) for improved versus worsened and no change versus worsened, respectively, P=0.003).

Change in Risk Group and CRT Response

Risk group at baseline was not associated with response (high vs. low HR: 0.38, CI: 0.11–1.30, intermediate vs. low HR 0.7, CI: 0.40 vs.1.26, p=0.198). However, a worsened biomarker risk group by 6 months negatively associated with response by univariate logistic regression. Patients who had improved or no change in risk group had significantly higher odds of being responders compared to those who had worsened (improved vs. worsened HR 20.6, CI 2.4 – 178.2, no change vs. worsened HR 15.7 CI 1.98–124.4, p=0.023). In addition to change in risk group, the multivariate model included the following baseline variables: Gender, creatinine, ischemic etiology, prior myocardial infarction, atrial fibrillation and diabetes. Worsened risk group from baseline to 6 months remained significant (improved versus worsened HR 24.3, CI 2.73 – 217, no change versus worsened HR 20.18, CI 2.49 – 163.9, p=0.015). In the multivariate model atrial fibrillation and diabetes remained significantly associated with response to CRT.

Risk Group and Incidence of Shocks

Among the cohort of 267 patients, there were a total of 98 shocks from 22 patients (9 from the intermediate group and 13 from the low risk group). Of those only 16 shocks from 8 patients (3 from the intermediate risk group and 5 from the low risk group) were appropriate from ventricular arrhythmia while the majority were inappropriate due to supraventricular arrhythmia. No shocks were reported from the high risk group. Based on the generalized linear mixed effect model there was no correlation between risk group at baseline and the occurrence of appropriate or inappropriate shocks (p=0.52).

Discussion

In this prospective multicenter study we found that TnT and BNP, two commonly measured biomarkers, alone and in combination were associated with heart failure outcome among patients receiving CRT-D for appropriate indications. Patients in whom either biomarker level was above predetermined cut points (TnT = 0.01ng/ml, BNP = 440pg/ml) were more likely to meet the combined outcome of mortality or HFH during the one year follow up for the study. On univariate analysis the risk was high when either one of the biomarkers were elevated compared to those in whom neither were elevated. The risk was highest among those in whom levels of both biomarkers were increased. On multivariate analysis, the risk associated with high risk category held true after adjustment for other covariates. Furthermore, worsened risk group by six months was found to have significant negative association with both the primary outcome and CRT response.

BNP and Troponin-T have both been recognized to be released in patients with chronic heart failure particularly with reduced ejection fraction. They represent different responses to the stress associated with cardiomyopathy. BNP is an active peptide cleaved from its precursor pro-BNP and released largely in response to myocardial stretch. Low level troponin release

associated with cardiomyopathy has been ascribed to release of cytosolic protein due to membrane leak by stressed cells or to continual myocardial cell necrosis. It is plausible therefore to see a complimentary role for each of these in assessing the severity of heart failure. Elevated levels of BNP have been associated with worse outcome across multiple studies of heart failure both in the ambulatory setting and in association with acute decompensation. Likewise, troponin release has been associated with impaired hemodynamics, elevated wedge pressure and worse outcome.[12] Detectable TnT at baseline was found to portend the same poor prognosis among patients with cardiomyopathy and heart failure receiving an implantable defibrillator.[15] Either of the biomarkers have been demonstrated to improve with successful therapy and such improvement has been found to predict better outcome.[16,17] In combination, Troponin subtypes and BNP have been found to be associated with outcome among ambulatory heart failure patients.[13] Such a study among patients receiving CRT-D therapy, however, has been hitherto lacking.

A number of studies have demonstrated the utility of BNP levels (or the corresponding N terminal peptide; NT-proBNP) obtained at baseline or shortly after implant in assessing outcome for patients after CRT implant.[16–20] With few exceptions, these have been either single center, retrospectively designed, relatively small numbered, with shorter follow up time or lacking adjustment for covariates. Despite these limitations and the variability in endpoints or BNP level cut points derived for the studied cohorts, association of worse outcome with higher BNP levels has been a consistent finding. Similar studies have also demonstrated improvement in the biomarker profile with CRT and the association of such improvement with better outcome.[21–24] Findings from the CARE-HF trial are particularly relevant.[25,26] Richardson et al. reported that among all patients enrolled in the study at a mean follow up time of 29.4 months, elevated NT-BNP at baseline along with ischemic etiology of cardiomyopathy and severe MR associated with the primary outcome of the trial that being mortality and cardiovascular hospitalization irrespective of assignment to CRT. Interestingly, and in close parallel to our own findings, baseline NT-BNP did not associate with clinical benefit from CRT.[25] In a separate report on the same cohort followed for a mean duration of 37.6 months, Cleland et al. found that among 15 pre-specified baseline variables and 8 markers of response at 3 months, persistently elevated NT-pBNP and severe mitral regurgitation at 3 months were associated with all-cause mortality regardless of assignment to CRT. We find this information to complement our findings that change in risk category at six months based on the combined biomarkers associated with the primary outcome of HFH or death as well as with response to CRT. A recently published report from the MADIT CRT trial tells of the usefulness of BNP levels among patients with less advanced heart failure in predicting response to CRT.[27] Similar to our findings of an association of subsequent improvement in biomarker profile with response to CRT, in the MADIT CRT trial report, CRT recipients demonstrated significantly larger decreases in BNP levels at one year compared to patients randomized to ICD implant which was particularly evident among those who responded to CRT.

By contrast, there are few studies of the prognostic role of troponins among defibrillator recipients with or without CRT. In a single center study, Aarones et al. found lower troponin levels among CRT recipients at baseline to be associated with response to CRT and freedom from adverse cardiovascular outcome measures.[28]

Our study extends the findings above by demonstrating a value to obtaining levels of both biomarkers. A gradation of risk is demonstrated according to the combined levels at baseline. Patients with elevation of either biomarker level had an increased risk of meeting the primary outcome measure while patients in the highest risk category at baseline exceeded 7 fold the risk of meeting the primary outcome measure, while those in the intermediate group had double the risk. Moreover, we found value in repeat risk assessment. Patients whose risk category worsened were at a disadvantage in terms of primary outcome and CRT response. The biomarkers appear to reflect pump function at baseline and subsequent improvement with CRT. It is possible that among certain subsets, cardiomyopathy is too far advanced that CRT cannot be useful. Our study suggests that readily available biomarkers BNP and troponin may help identify such patients. The relationship between biomarker profile and arrhythmic risk has not been previously explored. Our findings do not support a role for the combined biomarkers in predicting arrhythmic risk. Rather, the difference in mortality among risk groups would appear to reflect excess due to pump failure.

There are several limitations to our study. Accrual of a relatively small number of patients took a long time and the distribution of patients among categories did not follow our initial projections with only a minority of the cohort falling into the high risk group. On the other hand, outcome events were relatively few, particularly in the case of defibrillator shocks. This and issues of co-linearity affected multivariate analysis results where QRS or baseline creatinine displaced risk group in stepwise multivariate analysis for the primary or one of the secondary outcome measures, respectively. This is not surprising as QRS and baseline creatinine have been repeatedly demonstrated to be strong predictors of outcome with CRT and does not negate the main finding of a potential role for biomarker profile in informing subsequent outcome with CRT. Residual measured or unmeasured confounding may have influenced these findings. Baseline risk was ascribed based on a single measurement of biomarker level at a time when patients were clinically stable. It is possible an average of multiple measurements would have yielded different results. Defibrillator shock analysis in absence of preset programmed parameters is inevitably limited. The paucity of defibrillator shocks among the highest risk patients may have been artificial as arrhythmias may have been terminal and not recorded on subsequent visits. This highlights the importance of incorporating remote device interrogation in future studies. Recognizing these limitations and that of the small numbers involved, this finding raises the possibility of utilizing CRT pacer in place of defibrillator among patients with highest risk biomarker profile.

In conclusion, in a multicenter prospective observational study, use of combined biomarkers successfully ascribed risk category to a cohort of CRT-D recipients. Risk category at baseline or subsequent change was associated with the primary outcome measure as well as response to CRT. Further studies exploring the potential role of traditional and novel biomarkers, particularly in combination, in monitoring and predicting CRT usefulness are warranted.

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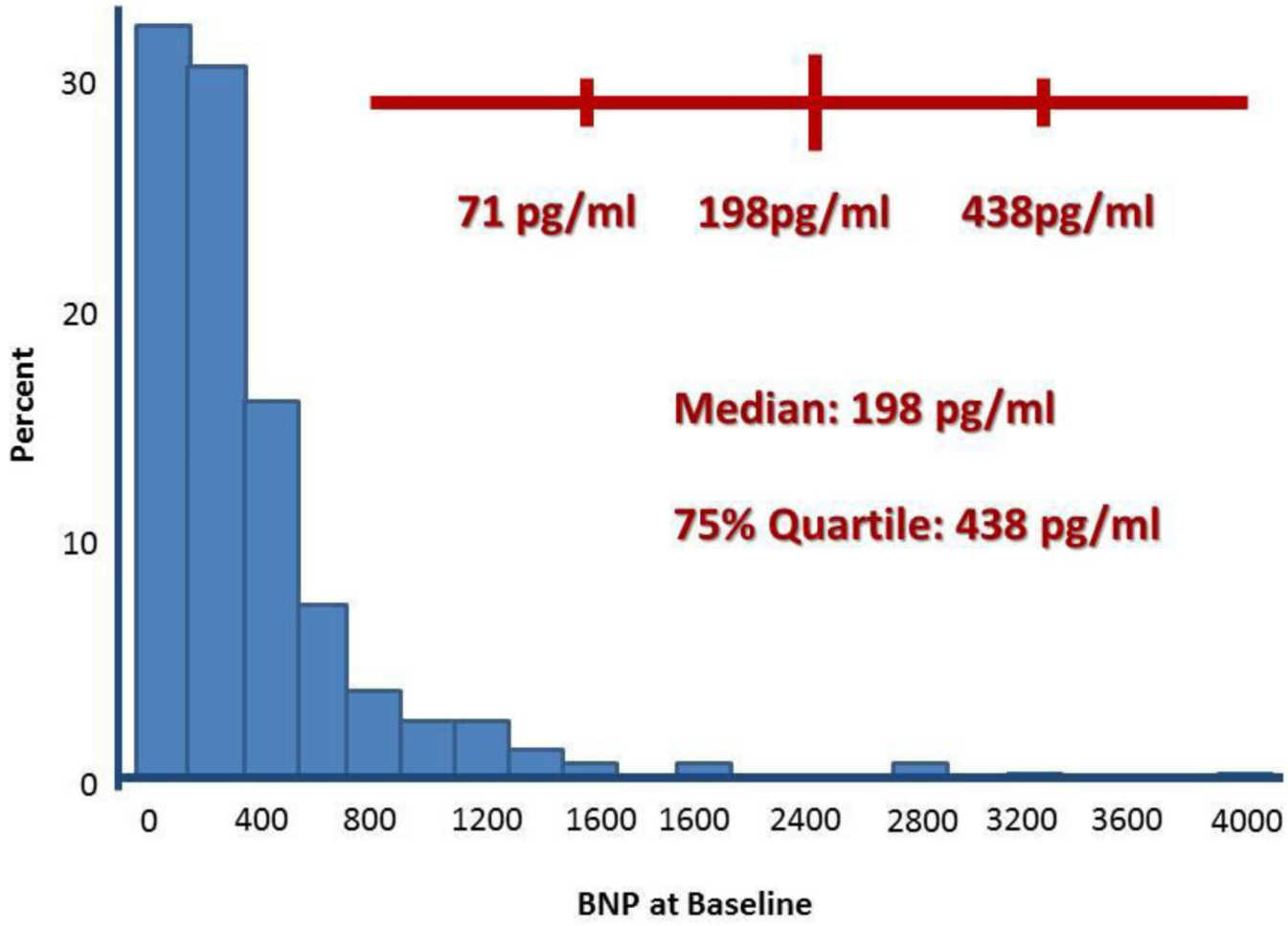


Figure 1.
Distribution of baseline BNP level distribution among the study cohort.

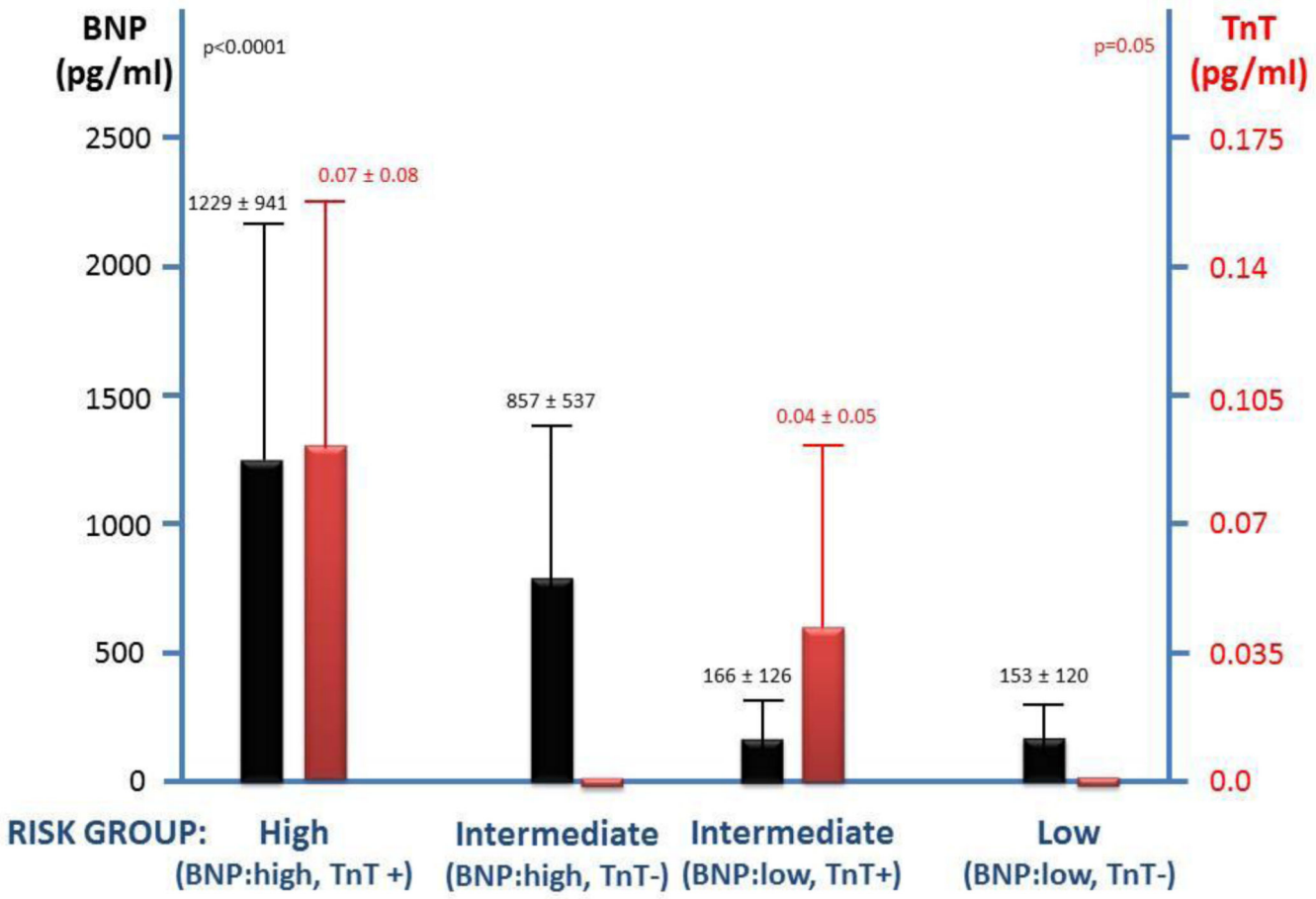
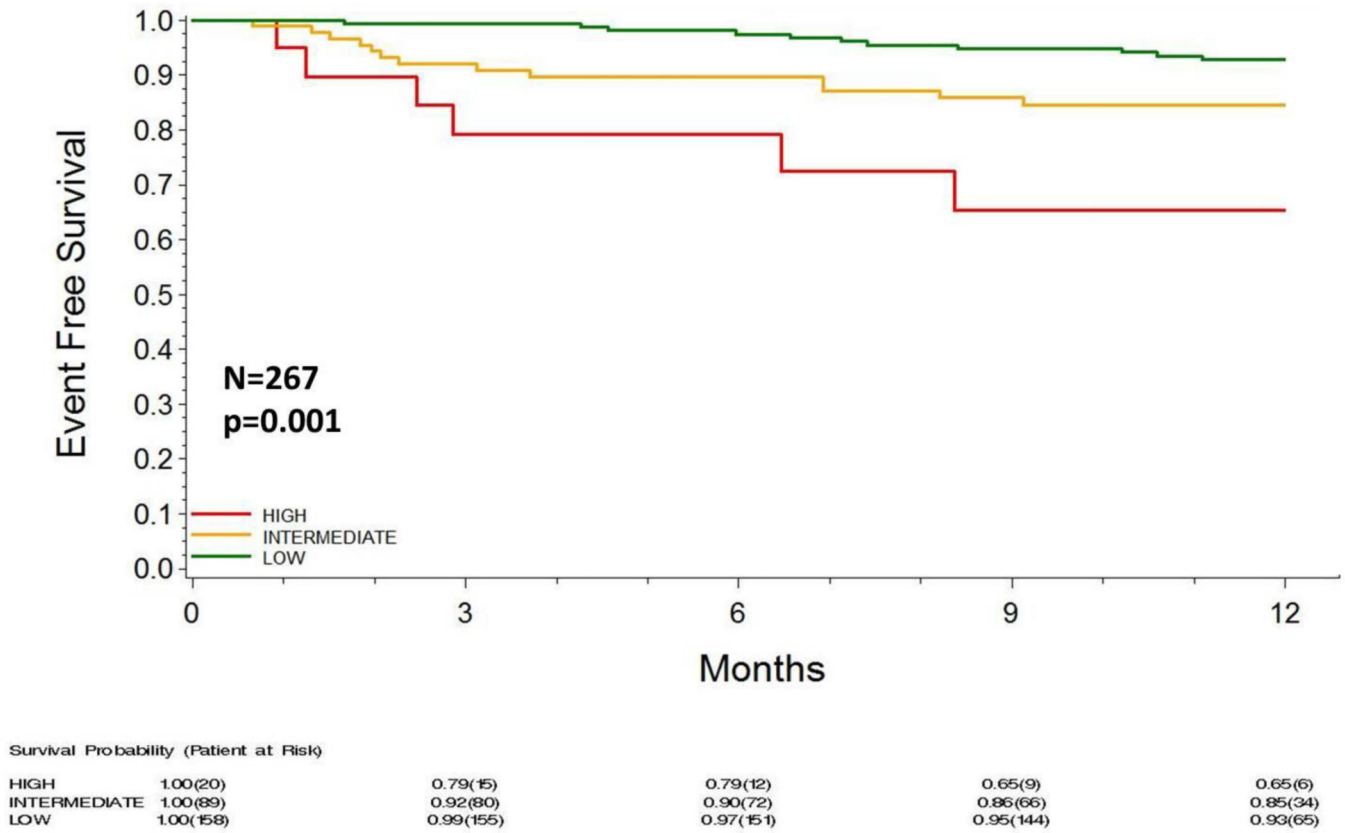


Figure 2.

Graph bar demonstrating the distribution of biomarker levels among risk groups (BNP levels:Black bars; TnT: Red). High risk group, had BNP >440pg/ml *and* detectable TnT (>0.01ng/ml). Patients fell into the intermediate group based on elevation of either BNP or detectable TnT (TnT +). Low risk group patients have no detectable TnT and BNP levels fall short of the cutpoint. ANOVA tests for BNP across groups: p=0.0001; for TnT between high risk and intermediate (TnT+) p = 0.05.



Survival Probability (Patient at Risk)

HIGH	1.00(20)	0.79(15)	0.79(12)	0.65(9)	0.65(6)
INTERMEDIATE	1.00(89)	0.92(80)	0.90(72)	0.86(66)	0.85(34)
LOW	1.00(158)	0.99(155)	0.97(151)	0.95(144)	0.93(65)

Figure 3.

KM analysis of freedom from the combined endpoint of heart failure hospitalization or death for three risk groups as determined by biomarker levels at baseline.

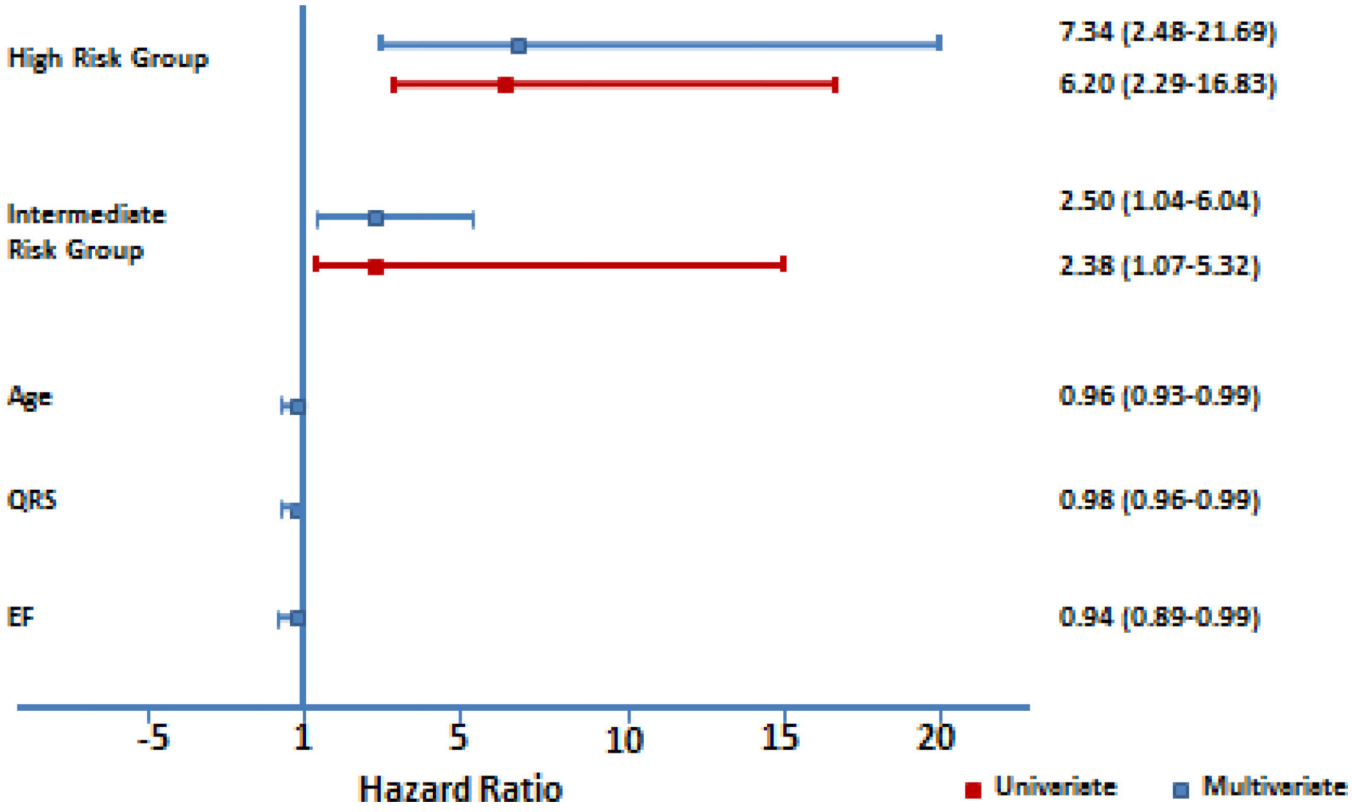


Figure 4.
Results of multivariate analysis for the primary endpoint of freedom from HFH and death.

Table 1

Patient Characteristics by Risk Group.

	Whole Cohort (N=267)	High (N=20)	Intermediate (N=89)	Low (N=158)	p-value
Age (years, mean ± SD)	66 ± 12	67 ± 15	67 ± 12	65 ± 11	0.233
Male	213 (79.8%)	19 (95.0%)	71 (79.8%)	123 (77.8%)	0.198
Ejection Fraction (%, mean ± SD)	25 ± 8	23 ± 7	24 ± 8	26 ± 7	0.181
QRS (msec, mean ± SD)	155 ± 26	161 ± 28	154 ± 27	155 ± 25	0.714
NYHA Class, n (%)					0.175
I	8 (3.0%)	0 (0.0%)	0 (0.0%)	8 (5.1%)	
II	37 (13.9%)	1 (5.0%)	11 (12.4%)	25 (15.9%)	
III	202 (75.9%)	17 (85.0%)	71 (79.8%)	114 (72.6%)	
IV	10 (3.8%)	2 (10.0%)	4 (4.5%)	4 (2.5%)	
Cardiovascular History, n (%)					
Ischemic	139 (52.1%)	10 (50.0%)	54 (60.7%)	75 (47.5%)	0.134
MI	108 (40.4%)	10 (50.0%)	36 (40.4%)	62 (39.2%)	0.653
CABG	104 (39.0%)	11 (55.0%)	38 (42.7%)	55 (34.8%)	0.147
PAF	52 (19.5%)	6 (30.0%)	19 (21.3%)	27 (17.1%)	0.335
Medical Comorbidity n (%)					
Diabetes	48 (18.0%)	2 (10.0%)	15 (16.9%)	31 (19.6%)	0.541
Hypertension	184 (68.9%)	15 (75.0%)	59 (66.3%)	110 (69.6%)	0.716
Creatinine (mg/dl; mean ± SD)	1.3 ± 0.5	1.5 ± 0.5	1.3 ± 0.6	1.2 ± 0.4	0.015
Pharmacologic Therapy, n (%)					
ACE or ARB	226 (84.6%)	17 (85.0%)	70 (78.7%)	139 (88.0%)	0.149
Beta Blockers	232 (86.9%)	13 (65.0%)	80 (89.9%)	139 (88.0%)	0.010
MLWHF (mean ± SD)	51 ± 26	57 ± 28	58 ± 25	47 ± 25	0.003
6-MHWT (feet, mean ± SD)	925 ± 351	837 ± 389	831 ± 361	989 ± 327	0.003

6-MHWT: Six minute hall walk test, ACE-I: Angiotensin converter enzyme inhibitor, ARB: Angiotensin receptor blocker CABG: Coronary artery bypass grafting, MLWHF: Minnesota living with heart failure questionnaire, PAF: Paroxysmal atrial fibrillation

Table 2

Distribution of endpoint events between risk groups:

	Deaths (%)*	HFH events (%) **	First event: Death or HFH (%) ***
Low (n=158)	6 (3.7)	5(3.2)	11 (7)
Intermediate (n=89)	5 (5.6)	10(11.2)	13 (15)
High (n=20)	2(10)	4(20)	6 (30)

* : p=0.29,

** : p=0.003,

*** p=0.005