Cardiotrophin-1 Predicts Death Or Heart Failure Following Acute Myocardial Infarction

Sohail Q Khan, Dominic Kelly, Paulene Quinn, Joan E Davies, Leong L Ng

University of Leicester

Department of Cardiovascular Sciences

Clinical Sciences Building

Leicester Royal Infirmary

Leicester

LE2 7LX

UK

Corresponding author: Dr. Sohail Q. Khan

Department of Cardiovascular Medicine

Clinical Sciences Building

Leicester Royal Infirmary

Leicester

LE2 7LX

UK

Phone:+1162523132 ; fax:+1162523108; e-mail:sqk1@le.ac.uk

Abstract

Background: Cardiotrophin-1 (CT-1) is an important inflammatory cytokine, its presence has been documented in patients following acute myocardial infarction (AMI). However its role as a predictor of death or heart failure is unclear. We sought to investigate this and compared it to N terminal pro B type natriuretic peptide (NT-proBNP), a marker of death or heart failure **Methods:** We studied 291 post AMI patients. The plasma concentration of CT-1 and NT-proBNP was determined using in-house non-competitive immunoassays and patients followed-up for death or heart failure **Results:** There were 27 deaths and 19 readmissions with heart failure. CT-1 was raised in patients with death or heart failure compared to survivors (median [range] fmol/ml, 0.9[0.1-392.2] vs. 0.67[0-453.3], p=0.019). Using a multivariate binary logistic model CT-1 (OR 1.8, 95% CI: 1.1-3.2, p=0.031) and NT-proBNP (OR 2.4, 95% CI: 1.1-5.2, p=0.026) predicted death or heart failure independently of age, sex, previous AMI, serum creatinine and Killip class. The receiver-operating curve for CT-1 yielded an area under the curve (AUC) of 0.62 (95% CI: 0.53-0.70, p=0.017) for NT-proBNP the AUC was 0.77 (95% CI: 0.69-0.86, p<0.001); the logistic model combining the 2 markers yielded an AUC of 0.84 (95% CI: 0.78-0.91, p<0.001). **Conclusion:** After an AMI, combined levels of CT-1 and NT-proBNP are more informative at predicting death or heart failure than either marker alone.

Keywords Myocardial infarction; heart failure; peptides; cardiotrophn-1; N terminal pro B type natriuretic peptide; prognosis

Introduction

Heart failure remains a leading cause of morbidity and mortality. The outcome of patients post myocardial infarction has improved somewhat due to advances in medical therapy, however the associated morbidity and mortality remains the same. Clinical features may be useful for predicting patients who are at risk of developing such complications post AMI but lack sensitivity and specificity. Biomarkers are emerging as a useful tool in predicting prognosis in patients after an AMI. B type natriuretic peptide and its more stable counterpart N terminal pro B type natriuretic peptide (NT-proBNP) have shown some promise in this area and are able to predict death or heart failure.[1] Newer peptides are emerging which may be of some use, particularly in a multi-marker strategy with NT-proBNP.

Cardiotrophin-1 (CT-1) is a 201 amino-acid inflammatory cytokine, which belongs to the interleukin-6 family. [2] CT-1 induces cardiac myocyte hypertrophy, [3] adding sarcomeres in series rather than in parallel and leading to increased cardiac myocyte size due to an increase in cell length, with little change in width. [4] It binds to the glycoprotein 130 (gp130) and leukaemia inhibitory factor receptor. [5] The actions of CT-1 are dependent on receptor binding but it has been shown to have protective effects on adult rat or human cardiomyocytes when added prior to ischaemia and at reperfusion.[6, 7] When given to rats it causes a decline in blood pressure and a reflex increase in heart rate. [8] CT-1 has been shown to be raised in patients following an AMI and unstable angina [9,10] and in those patients with echocardiographic heart failure compared to controls. [11] Most recently CT-1 has been shown to be raised in hypertension. [12,13] It is unclear however whether CT-1 has a protective or detrimental effect in AMI as it triggers hypertrophy and anti-apoptotic pathways by distinct mechanisms. The role of CT-1 in the prognostication of AMI is unknown. In this

study we investigated whether CT-1 would be of benefit in determining the prognosis of AMI particularly death and heart failure which remain a leading cause of mortality and morbidity. We compared this with N terminal pro B type natriuretic peptide (NT-proBNP), which has been shown to be of prognostic benefit in this group of patients. [1,14,15]

Methods

Study population

We studied 291 consecutive acute myocardial infarction patients admitted to the Coronary Care Unit of Leicester Royal Infirmary. The study complied with the Declaration of Helsinki and was approved by the local ethics committee; written informed consent was obtained from patients. AMI was defined at presentation with at least two of three standard criteria, i.e. appropriate symptoms, acute ECG changes of infarction (ST elevation or depression, new left bundle branch block) and a rise in troponin T above the 99th centile for our population. AMI was sub categorised into ST segment elevation myocardial infarction (STEMI) or non-ST segment myocardial infarction (NSTEMI). Primary treatment for STEMI in our institution is thrombolytic therapy and was administered by the attending physician if the patient presented within 12 hours of symptom onset. Exclusion criteria were known malignancy, or surgery in the previous month. Control subjects (n=47) were age and gender matched and recruited from University of Leicester and had peptide measurements made on one occasion.

Plasma samples

Blood measurement was made at 25-48hrs after the onset of chest pain for determination of plasma CT-1 and NT-proBNP. After 15 minutes bed rest, 20mL blood was collected into tubes containing EDTA and aprotinin. All plasma was stored at -70°C until assayed in a single batch.

Echocardiography

Transthoracic echocardiography was performed in patients using a Sonos 5500 instrument (Philips Medical Systems, Reigate, UK). A 16-segment left ventricular wall motion index (LVWMI) based on the American Society of Echocardiography mode was derived by scoring each LV segment (1=normal, 2=hypokinesis, 3=akinesis and 4=dyskinesis (Paradoxical Motion), and dividing the total by the number of segments scored. Left ventricular ejection fraction (LVEF) was calculated using the biplane method of discs formula. [16] Inter and intra coefficients of variation were 9.3% and 11.4% respectively.

NT-pro**BNP assay**

Our NT-proBNP assay was based on a non-competitive assay. Sheep antibodies were raised to the N-terminal of human NT-proBNP and monoclonal mouse antibodies were raised to the C- terminal. The N-terminal IgG was affinity-purified and biotinylated. Samples or NT-proBNP standards were incubated in C-terminal IgG–coated wells with the biotinylated N-terminal antibody for 24 hours at 4°C. Detection was with methyl-acridinium ester (MAE)–labelled streptavidin. [17] The lower limit of detection was 0.3 fmol/ml. Inter and intra coefficients of variation were 2.3% and

4.8% respectively. There was no cross reactivity with atrial natriuretic peptide, BNP, or C-type natriuretic peptide.

CT-1 assay

The CT-1 assay was based on a non-competitive assay. ELISA plates were coated with anti-rabbit IgG (100ng/well). The capture antibody was a rabbit anti-CT-1 antibody (100ng/100μL assay buffer, Peprotech Inc, Rocky Hill, NJ), and detection employed a biotinylated mouse monoclonal antibody (50ng/100μL assay buffer, BioVendor Laboratory Medicine, Modrice, Czech Republic). Plasma samples (50 μL) or CT-1 standards were incubated for 24 hours at 4°C. Following washes; detection was performed using methyl-acridinium ester (MAE)–labelled streptavidin. Intra- and inter- assay coefficients of variation were found to be less than 10%.

End points

We assessed the value of both CT-1 and NT-proBNP for the prediction of death or heart failure. A combined primary endpoint consisting of death and rehospitalization for heart failure was used. Hospitalization for heart failure was defined as a hospital admission for which heart failure was the primary reason and was verified by contacting each patient and review of their notes. Death endpoints were obtained by reviewing the Office of National Statistics Registry which records all hospital deaths. There was a minimum 30-day follow-up of all patients.

Statistical analysis

Statistical analyses were performed on SPSS Version 12 (SPSS Inc, Chicago, Illinois). The continuous variables in the two independent groups were compared

using the Mann Whitney U test and results for continuous variables are displayed as median (range). Endpoints were analysed as categorical for CT-1 and NT-proBNP. Spearman's correlations were performed and binary logistic regression analyses were conducted which included baseline patient characteristics (age, sex, serum creatinine, Killip class, territory of AMI and whether the patient received thrombolysis or not) and peptide markers (including troponin I), to test the independent predictive power of the peptides above and below the median for death or heart failure as defined above. NT-proBNP and CT-1 were normalised by log transformation. Thus, odds ratios and hazard ratios refer to a tenfold rise in the levels of these markers. To identify the independent predictors of death or heart failure, Cox proportional hazard analyses was used. Kaplan Meier survival curves were generated to visualise the relationship between the peptides NT-proBNP and CT-1 and the primary endpoint as time to first event. To compare the predictive value of NT-proBNP and CT-1, receiver-operating characteristic (ROC) curves were generated at 438 days and the area under the curves (AUC) was calculated. A p value of less than 0.05 was deemed to be statistically significant. Power calculations showed that for a 2.5 fold difference in CT-1 values between those with the primary endpoint and the event free group, the number of patients needed was 266 to detect a difference with a power of 90% at $p<0.05$.

Results

Patient characteristics

The demographic features of the patient population are shown in Table 1. Median length of follow-up was 336 days with a range of 0–645 days. Of the patients enrolled, 153 (52.6 %) received thrombolysis during the index admission. No patient

was lost to follow-up. During follow-up, 27 (9.3%) patients died and 19 (6.5%) were readmitted with heart failure. Echocardiographic data was available for 252 (86.6%) of the 291 patients and done at median of 3.5 days (range 2-5) after presentation with AMI. 22 echocardiograms were not analysable and 17 patients did not receive an echocardiogram. A subset of 50 patients had daily samples taken to determine the secretion profile of the respective peptides. The cohort was randomly selected and there was no identifiable significant differences noted in this group compared to the main group in terms of age, sex, PMH, location of infarct or LVWMI.

CT-1 levels in patients and controls

Plasma levels of CT-1 in patients with AMI ranged from 0.03- 453.3fmol/ml with a median of 0.77fmol/ml. CT-1 was higher in patients following AMI compared to control subjects (median [range] fmol/ml 0.77[0.03-457.1] vs. 0.73[0.20-1.78], p=0.001). CT-1 was significantly higher in patients who died (median [range] fmol/ml 0.88[0.2–294.1] vs. 0.70[0.03– 453.3], p=0.05). The time course of secretion of CT-1 was measured daily in a subset of 50 patients revealing a significant overall difference in secretion over the 5 days ($p<0.0001$). There was also a significant difference in secretion when day 1 was compared to days 2, 3 and 4 ($p<0.0001$) and is shown in figure 1.

There was no correlation of CT-1 with age ($r= 0.07$, $p= 0.228$), LVWMI ($r= -0.042$, $p= 0.507$) or heart failure ($r= 0.064$, $p> 0.346$). CT-1 did not differ significantly according to gender, smoking status, the presence or absence of diabetes mellitus, hypertension, previous MI diagnosis, hypercholesterolemia or whether a patient received thrombolyis or not. There was no correlation however between NT-proBNP and CT-1 ($r=0.087$, $p=0.138$).

NT-pro**BNP levels in patients and controls**

NT-proBNP was significantly elevated in AMI compared with controls (Median [Range], fmol/ml, 1459.9[0.3–11906.5] vs. 10.1[0.3– 134.4], p<0.0001) and was significantly higher in patients who died (median [range] fmol/ml 6727.2[20.1–11906.5] vs. 1228.3[0.30– 10800.14], p<0.001) or were readmitted with heart failure (median [range] fmol/ml 4678.15[353.47 – 10712.99] vs. 1367.47[0.3–11906.47], p=0.012). The time course of secretion of NT-proBNP revealed a significant overall difference in secretion over 5 days (p<0.0001) in a 50 patient sample and is shown in figure 2.

Relationship between CT-1 and echocardiographic parameters

For the whole population, mean LVWMI was 1.52 (range 1.08-2.75) and EF was 38% (range 12-49%). The LVWMI score in those subjects with anterior AMI was higher than in those with inferior AMI (median [range] fmol/ml 1.7 [1.08-2.75] vs. 1.4 [1.00-2.60], p<0.0001). However LVEF was no different between the two groups (median [range] fmol/ml 39 [12-68] vs. 40 [13-65]) %, p=0.45). There was a weak correlation of CT-1 with LVWMI (r= 0.125, p= 0.049). NT-proBNP also correlated positively with LVWMI (r=0.35, p<0.0001) and negatively with the EF (r= -0.30, p<0.0001).

CT-1 and NT-pro**BNP as predictors of death or heart failure**

CT-1 was raised in patients with death or heart failure compared to survivors (median [range] fmol/ml, 0.9[0.05-392.2] vs. 0.67[0.03-453.3], p=0.019). There was no significant difference in CT-1 between patients who died or were readmitted with heart failure (median [range] fmol/ml, 0.88[0.2–294.1] vs. 0.93[0.05-389.0], p=NS).

When clinical and demographic characteristics were entered into a multivariate binary logistic model CT-1 (OR 1.8, 95% CI: 1.1-3.2, p=0.031) and NT-proBNP (OR 2.4, 95% CI: 1.1-5.2, p=0.026) independently predicted the primary endpoint. This was also confirmed on the Cox proportional hazards model with the independent predictors of death or heart failure being CT-1 (HR 1.5, 95% CI: 1.1-2.0, p=0.034) and NT-proBNP (HR 2.1, 95% CI: 1.0-4.3, p=0.05)

The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with CT-1 below the median compared with those with CT-1 above the median (log rank 5.79, p=0.016, figure 3). This was also true for NT-proBNP (log rank 20.24, p<0.0001, figure 4). The receiver-operating curve for CT-1 yielded an area under the curve (AUC) of 0.62 (95% CI: 0.53-0.70, p=0.017); for NT-proBNP the AUC was 0.77 (95% CI: 0.69-0.86, p<0.001). The logistic model combining the 2 markers (predicted probability) yielded an AUC of 0.84 (95% CI: 0.78-0.91, p<0.001), which exceeded that of either peptide alone (figure 5).

Discussion

Reperfusion therapy has improved mortality post MI, however the outcome of patients despite this is still poor; [18] for this reason risk stratification remains important and may be useful in helping to select treatment regimes in the future. A multimarker strategy has benefits in that it utilizes the different pathways that are involved in the development and outcome of an AMI in the hope that complementary information can be gained. [19] The aim of this study was to assess the utility of CT-1 and NT-proBNP in determining the prognosis of AMI patients. The results of this study confirm the independent prognostic values of early CT-1 and NT-proBNP levels in determining death or heart failure in patients who have an AMI. The information has been gained

with a single blood test taken between 25-48 hours. Unlike NT-proBNP there was no correlation of CT-1 with age or sex, which may make it a more discerning marker. The predictive value of CT-1 provides risk prediction independent of NT-proBNP and other known clinical predictors of death or heart failure. Both CT-1 and NT-proBNP are raised after an AMI and their secretion patterns differ over the 5 days following an AMI with significant differences noted for both peptides. CT-1 is raised early after an AMI with levels falling rapidly after the first 24 hours then rising again. This suggests that there may be a stored pool of CT-1, which is released after an AMI, with the second wave of release due to new synthesis of the peptide. The likely source of CT-1 is unknown however a possible source is the left ventricle. We have shown a weak but positive correlation between CT-1 and LVWMI. Other possible sources could well be the atria; CT-1 has been shown to be raised in the atrial tissue of WKY rats. [13]

We used CT-1, an inflammatory cytokine and NT-proBNP, which is a more stable by-product in the production of BNP. [20] We have clearly shown the benefit of using each peptide alone at predicting death or heart failure; indeed NT-proBNP is a well-established marker for predicting LV dysfunction and prognosis after an acute myocardial infarction. [1] Using a combination of CT-1 and NT-proBNP in a multi-marker risk stratification approach in patients gives an increased area under the ROC curve and more predictive accuracy.

The relationships for prediction exists in quite a heterogeneous group of patients (NSTEMI, STEMI, previous history of cardiovascular diseases and age etc) it would be interesting to see if a separation could be made on the basis of presenting diagnosis. What also remains to be seen is the utility of CT-1 at being able to individually predict death or heart failure however a larger powered study would be necessary to answer such a question.

In conclusion, this is the first report of CT-1 as a prognostic marker of death or heart failure in patients with AMI. This study confirms previous findings that CT-1 is involved during an AMI and it may be useful in a multimarker approach with NT-proBNP for risk stratification in AMI patients.

Acknowledgments

Dr Sohail Q Khan is supported by a British Heart Foundation Junior Research Fellowship (FS/03/028/15486). We thank Sonja Jennings for expert technical assistance.

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Legends

Figure 1 Time dependent changes in CT-1 (mean ± SEM) after onset of AMI

Figure 2 Time dependent changes in NT-proBNP (mean ± SEM) after onset of AMI

Figure 3 Kaplan-Meier Curve: Time to death or heart failure related to serum CT-1

Figure 4 Kaplan-Meier Curve: Time to death or heart failure related to serum NT-proBNP

Figure 5 Combined Receiver Operating Curve comparing NT-proBNP, CT-1 and the combined predicted probabilities of death or heart failure

Table 1 Characteristics of patients and controls in the study. Values are means (SD) or numbers (percentage)

	Controls	AMI Patients
Number	47	291
Age (in years)	61.8 ± 13.7	64.0 ± 12.9
Male Sex	30 (63.8)	227 (78.0)
Previous Medical History		
Myocardial infarction	None	41 (14.1)
Angina Pectoris	None	54 (13.5)
Hypertension	None	125 (44.3)
Diabetes mellitus	None	63 (20.6)
Hypercholesterolaemia	None	87 (28.1)
Obesity	None	42 (15.4)
Current/Ex-Smokers	None	101 (36.7)
ST-elevation AMI	None	220 (75.6)
Thrombolytic	None	153 (52.6)
Territory of Infarct		
Anterior		125 (43.0)
Inferior		140 (48.1)
Other/undetermined		26 (8.9)
Killip Class on Admission		
I		143 (49.1)
II		119 (40.9)
III		25 (8.6)

IV		4 (1.4)
Peak CK (IU)		1251.9 ± 1401.1
Peak Troponin I (ng/ml)		20.4 ± 31.2
Creatinine (µmol/l)		102.2 ± 35.2

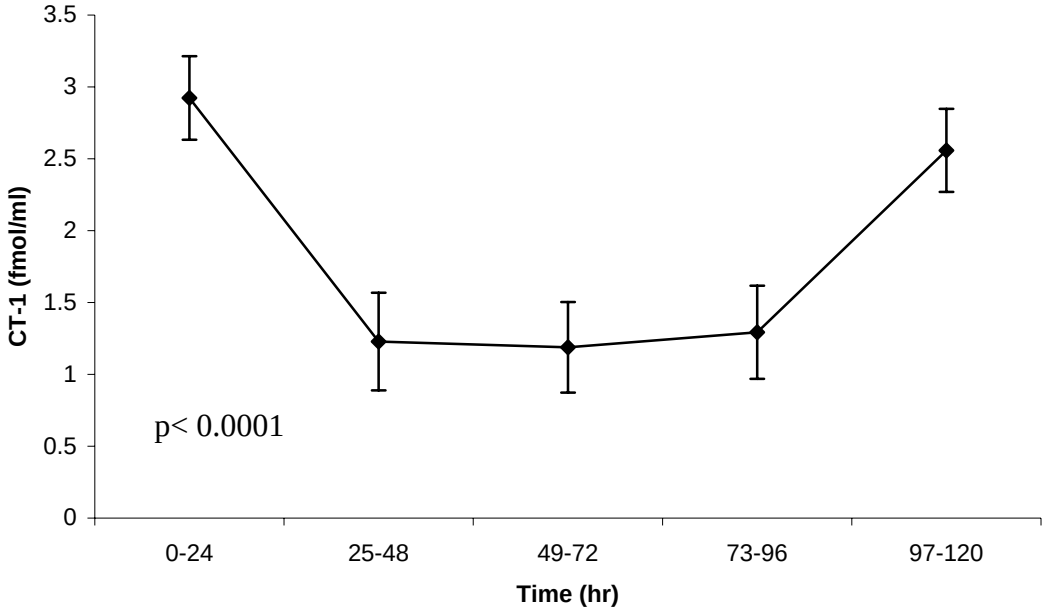
3.5
3
2.5
2
1.5
1
0.5
0
CT-1 (fmol/ml)
p< 0.0001
0-24
25-48
49-72
73-96
97-120
Time (hr)

Figure 1

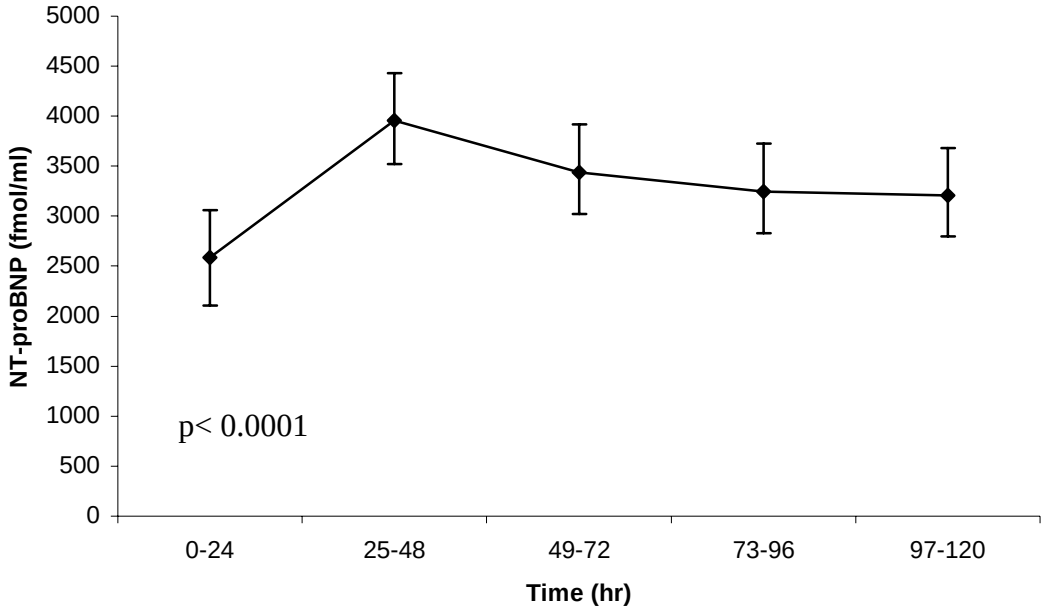
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
NT-proBNP (fmol/ml)
p< 0.0001
0-24
25-48
49-72
73-96
97-120
Time (hr)

Figure 2

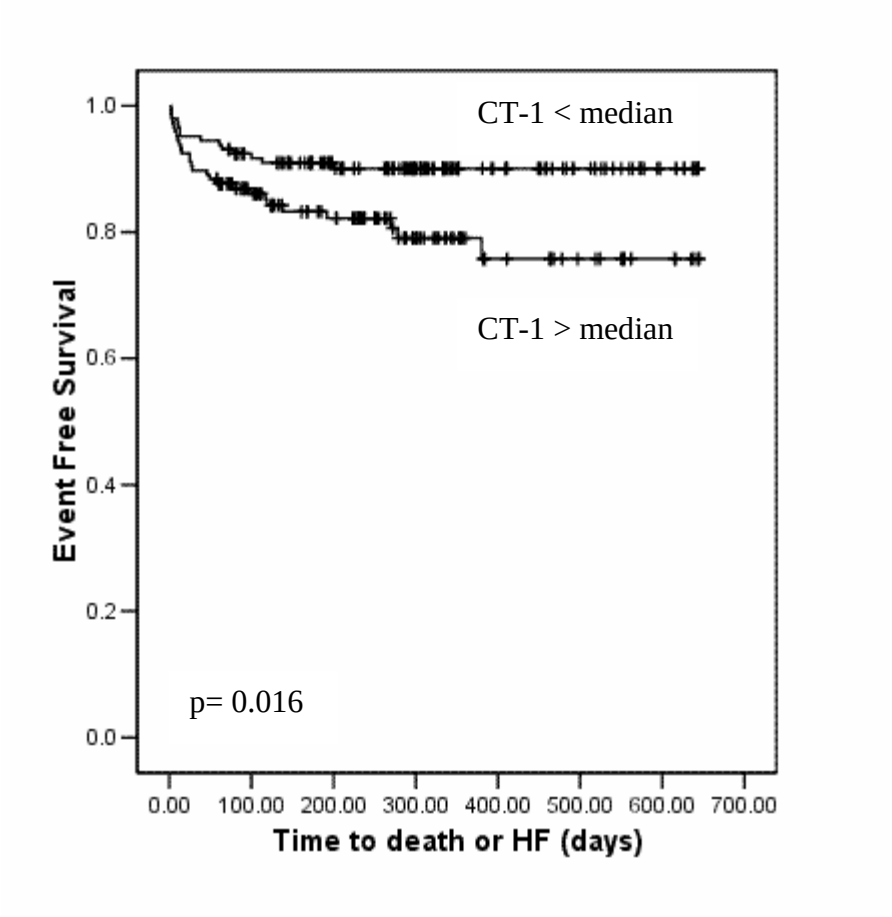
CT-1 < median
CT-1 > median
p= 0.016
Event Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
100.00
200.00
300.00
400.00
500.00
600.00
700.00
Time to death or HF (days)

Figure 3

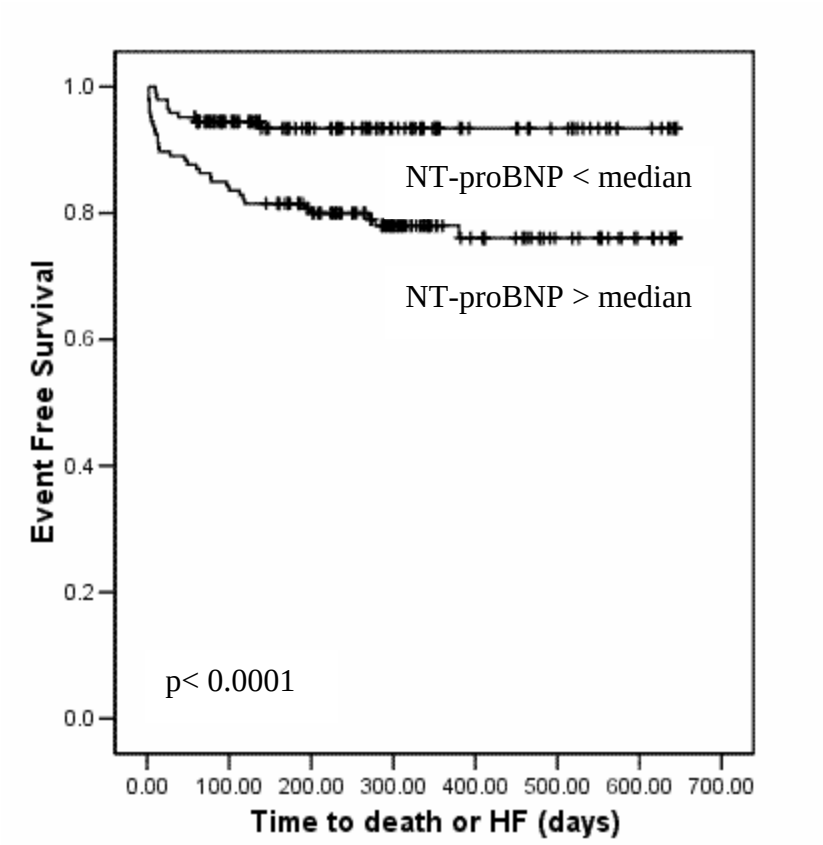
1.0
0.8
0.6
0.4
0.2
0.0
Event Free Survival
NT-proBNP < median
NT-proBNP > median
p< 0.0001
0.00
100.00
200.00
300.00
400.00
500.00
600.00
700.00
Time to death or HF (days)

Figure 4

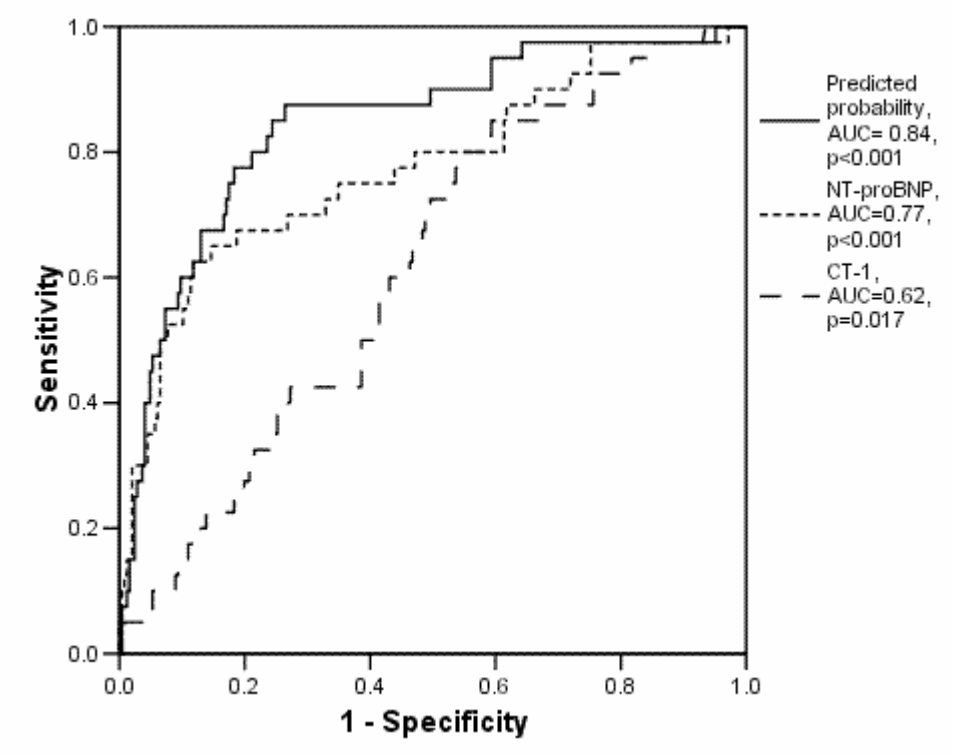
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Predicted probability, AUC= 0.84, p<0.001
NT-proBNP, AUC=0.77, p<0.001
CT-1, AUC=0.62, p=0.017

Figure 5