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Brain natriuretic peptide is associated with survival in persons with dysvascular major lower limb amputation

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ABSTRACT

Brain natriuretic peptide (pg/ml) is a cardioprotective hormone released in response to pressure or volume overload of the heart. High preoperative brain natriuretic peptide levels in persons with dysvascular major lower limb amputation may indicate cardiac stress threatening survival. The aim of this retrospective database study was to analyze the association between brain natriuretic peptide, heart failure and survival in persons with dysvascular major lower limb amputation.

Data of persons with dysvascular major lower limb amputations, at Nij Smellinghe Hospital (2010 to 2018), were included. Brain natriuretic peptide levels, determined pre- and/or post-amputation, were collected. Persons were categorized in two groups: 'low' brain natriuretic peptide (≤91 pg/ml) and 'high' brain natriuretic peptide (>91 pg/ml).

Data of 59 persons (median age 73, interquartile range 66;80, 42 males) were included. Survivors had a significantly lower preoperative brain natriuretic peptide level (median 46, interquartile range 21;75) compared to non-survivors (median 135, interquartile range 38;316, Mann-Whitney U Test: p=0.029) and postoperative brain natriuretic peptide levels (median 26, interquartile range 16;42) compared to non-survivors (median 176, interquartile range 61;323, p=0.007). The 'low' brain natriuretic peptide group lived significantly longer (median 2305 days, interquartile range 1361;2979) than the 'high' brain natriuretic peptide group (median 687 days, interquartile range 87;1224, Log Rank=20.843; Kaplan-Meier: p=<0.001). Persons with high brain natriuretic peptide and heart failure lived shorter than those with low brain natriuretic peptide and heart failure (Kruskal-Wallis Test: p=0.008) and those with low brain natriuretic peptide without heart failure (p=0.004). Survival was shortest in the group with the high brain natriuretic peptide levels and heart failure.

In this small study, brain natriuretic peptide levels, also combined with heart failure, were associated with survival in persons with a major lower limb amputation.

Introduction

Most lower limb amputations are secondary to diabetes mellitus (DM) and/or peripheral arterial disease (PAD).[1] Mortality rates after major lower limb amputations (mLLA, all levels proximal to the ankle joint) are high.[2-5] The 5-year mortality in persons with mLLA ranges from 52% to 80%.[5] Myocardial infarction or heart failure (HF) are common perioperative complications in persons with a mLLA.[6]

Brain natriuretic peptide (BNP in pg/ml), a cardioprotective hormone, is released by cardiomyocytes in response to volume overload or pressure indicative for cardiac stress in case of ventricular dysfunction or HF.[7] In persons with open reconstructions with PAD, elevated preoperative BNP levels (>100 pg/ml) are associated with major adverse cardiovascular events.[8] In octogenarians with critical limb ischemia, preoperative BNP levels ≥500 pg/mL are associated with mortality, independently of confounders.[9] High preoperative BNP levels in persons with dysvascular mLLA may indicate the presence of cardiac stress possibly threatening survival after amputation.

For the post-amputation rehabilitation, cardiac function is important because persons with a mLLA have significantly higher energy expenditure during gait compared to people without an amputation.[10-11] These higher energy costs of walking after a mLLA increases cardiac stress and load, potentially leading to cardiac complications during rehabilitation training, particularly in case of pre-existing HF. Individualized rehabilitation training programs can minimize the risk of these complications. Cardiovascular disease is associated with a reduced likelihood of achieving independent prosthetic ambulation (39% for individuals with cardiovascular disease versus 76% for those without) and with poorer functional and mobility outcomes.[12-13] Many individuals with mLLA and cardiovascular disease have a low physical fitness, which can result in decreased activity levels and participation.[13-14] Therefore it is important to start rehabilitation in a safe and efficient manner to improve physical fitness.[15]

Very limited research is available on BNP levels in the mLLA population. One pilot study explored the association between preoperative N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker for serious ventricular dysfunction, and survival. Preoperative NT-proBNP levels were higher in non-survivors than in survivors, but the reported difference was not significant.[16] Although NT-proBNP is also a marker for HF with a high sensitivity,[17-18] NT-proBNP depends more on renal function compared to BNP.[18] For these reason, BNP may be more suitable for this research, as NT-proBNP and BNP have a similar diagnostic accuracy.[19]

The predictive value of BNP was investigated in 41 patients undergoing major vascular surgery (of whom 13 had an amputation, levels of amputation unclear). Fourteen patients had a preoperative BNP level of 100 pg/ml or more. In 11 of them (79%) a perioperative cardiac event occurred. In the remaining patients (BNP < 100 pg/ml) no cardiac events were observed. Forty-six percent of the patients with an amputation (with a median BNP level of 121 pg/ml) experienced a cardiac event.[20]

Despite its potential clinical relevance, BNP has not been adequately evaluated for its association with survival after amputation in combination with HF. Therefore this retrospective database study aimed to analyze the association between pre- and postoperative BNP levels, survival and HF in persons with dysvascular mLLA.

Methods

Prior to data collection, this retrospective database study was approved by the Medical Ethics Committee of hospital Nij Smellinghe in Drachten, the Netherlands (approval number: BK/HdJ/ ID 14954). The Medical Ethics Committee judged that obtaining informed consent was not reasonably possible conform the Medical Treatment Contracts Act (Dutch Law 'Wet geneeskundige behandelsovereenkomst', article 458).

Inclusion criteria for this study were 18 years and older at time of mLLA, a mLLA with an etiology of PAD and/or DM, amputated between January 1, 2010 and December 31, 2018, and BNP level had to be determined at least once, preoperatively or postoperatively, within six months of the amputation.

From the included persons, the following data was extracted from the files; age, gender, Body Mass Index (BMI), BNP levels, medical history and amputation characteristics. Medical history was categorized into PAD, HF, hypertension, DM, renal disease, chronic pulmonary disease, hypercholesterolemia and cerebrovascular accident. Heart failure was dichotomized as yes or no. Amputation characteristics included date and level of amputation and date and level of any re-amputation. In case a person had more than 1 pre- or postoperative BNP level of measured, the levels closest to the amputation date, preoperatively or postoperatively, were used. The most recent preoperative BNP level and the first postoperative BNP level were recorded, including the date of the BNP measurements. Survival time was determined at February 17, 2023 in days from amputation.

STATISTICAL ANALYSIS

Descriptive statistics were provided for personal and medical characteristics and BNP levels. Categorical variables were presented as frequencies and column percentages. Non-normally distributed variables were reported as median and interquartile range (IQR). The Mann-Whitney U Test was used to analyze differences in pre- and postoperative BNP levels between survivors and non-survivors. The Mann-Whitney U Test was used to analyze differences in change (between pre- and postoperative levels) in BNP levels between survivors and non-survivors.

A Kaplan-Meier Test was performed to analyze the association between preoperative BNP levels and survival. The persons were categorized into a 'low' group (preoperative BNP level median and below) and a 'high' group (preoperative BNP level above the median). A Kaplan-Meier Test was also performed to analyze the association between HF and survival. Mann-Whitney U Tests were used to analyze the preoperative BNP levels between persons with and without HF and to analyze differences in change in BNP levels between persons with and without HF. Interaction effect of HF and BNP levels on survival was explored. Persons were divided into four groups: 1) low BNP without HF, 2) high BNP without HF, 3) low BNP with HF, and 4) high BNP with HF. Survival curves of these four group crossed each other and a Kruskal Wallis test (with post-hoc analysis with pair-wise comparisons and Bonferroni correction) was conducted to analyze survival in these groups. For the analyses International Business Machines Statistical Package for the Social Sciences (IBM SPSS) Statistics version 28 was used and for statistical significance α was set at 0.05.

Results

Data of 59 persons (17 women and 42 men) undergoing a mLLA in 2010-2018 were included in this study (Table 1). Thirteen were alive (survivors) at February 17, 2023. The median age at the time of amputation was 73 years (IQR 66;80). Median BMI before amputation was 25 kg/m^2 (IQR 22;29). In 76% of the persons PAD was present and DM in 42% of the persons. In the total group six transfemoral amputations, 25 knee disarticulations and 28 transtibial amputations were performed (Table 1).

Table 1: Characteristics of included persons

Characteristics of persons	Total group (n=59)	Survivors* (n=13)	Non-survivors (n=46)
Age in years, median (IQR)	73 (66;80)	69 (62;74)	73 (67;80)
Males, n (%)	42 (71)	9 (69)	33 (72)
BMI pre-amputation, median (IQR)	25 (22;29)	25 (23;30)	25 (22;29)
Medical history, n (%)			
- Peripheral arterial disease (PAD)	45 (76)	11 (85)	34 (74)
- Heart failure (HF)	34 (58)	6 (46)	28 (61)
- Hypertension	29 (49)	5 (39)	24 (52)
- Diabetes mellitus (DM)	25 (42)	5 (39)	20 (44)
- Renal disease	12 (20)	2 (15)	10 (22)
- Chronic pulmonary disease	10 (17)	1 (8)	9 (20)
- Hypercholesterolemia	5 (9)	2 (15)	3 (7)
- Cerebrovascular accident	10 (17)	2 (15)	8 (17)
Number of comorbidity, median (IQR)	3 (2;4)	3 (2;4)	3 (2;4)
Characteristics of amputation			
Level of amputation, n (%)			
- Transfemoral	6 (10)	1 (8)	5 (11)
- Knee disarticulation	25 (42)	4 (31)	21 (46)
- Transtibial	28 (48)	8 (62)	20 (44)
Reamputation, n (%)	10 (17)	1 (8)	9 (20)
- Transfemoral	4 (7)	0 (0)	4 (9)
- Knee disarticulation	3 (5)	1 (8)	2 (4)
Stump revision, (%)	3 (5)	0 (0)	3 (7)
Survival			
Survival duration, median (IQR)	1195 (357;2304)	2947 (2672;3530)	733 (189;1750)
1-year survival (%)	75	100	67
5-year survival (%)	37	100	20

IQR=interquartile range

* Survival determined at February 17, 2023

Survivors had a significantly lower preoperative BNP level (median 46, IQR 21;75) compared to non-survivors (median 135, IQR 38;316, p=0.029, Table 2). Survivors also had a significantly lower postoperative BNP level (median 26, IQR 16;42) compared to non-survivors (median 176, IQR 61;323, p=0.007). No significant difference was found in change of BNP levels, pre- and postoperatively, between survivors and non-survivors.

Table 2: BNP measurements in the total groups, survivors and non-survivors

Variables	Total group (n=59)	Survivors* (n=13)	Non-survivors (n=46)	p-value
Preoperative BNP	n=47	n=12	n=35	
BNP level in pg/ml, median (IQR)	91 (33;193)	46 (21;75)	135 (38;316)	p=0.029
Days before amputation determined, median (IQR)	1 (0;6)	1 (1;4)	1 (0;8)	
Postoperative BNP	n=40	n=5	n=35	
Median level in pg/ml, median (IQR)	138 (38;271)	26 (16;42)	176 (61;323)	p=0.007
Days after amputation determined, median (IQR)	3 (1;10)	1 (1;4)	3 (1;12)	
Change in BNP level (pre- vs postoperative)	n=28	n=4	n=24	
Median change in level in pg/ml, median (IQR)	15 (-2;141)	10 (0;19)	16 (-8;156)	p=0.555

IQR=interquartile range
* Survival determined at February 17, 2023

Persons in the 'low' BNP group lived significantly (Log Rank= 20.843; p=<0.001, median days 2305, IQR 1361;2979) longer than persons in the 'high' BNP group (median days 687, IQR 87;1224, Figure 1).

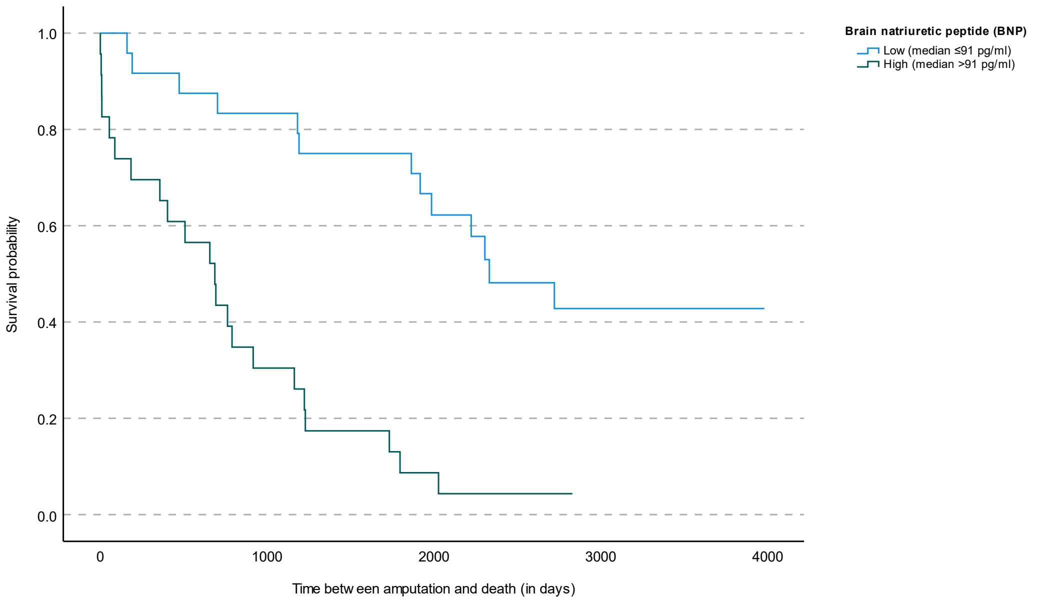

Figure 1: Survival analysis. The survival time was measured in days from the date of amputation until February 17, 2023. The analysis compares two groups based on brain natriuretic peptide (BNP) levels: those with low BNP (median ≤ 91 pg/ml, n=24) and those with high BNP (median > 91 pg/ml, n=23). The Log-Rank test showed a significant difference between the groups (Log-Rank = 20.843, p < 0.001).

The association between HF and survival was nearly significant (p=0.07). Persons without HF had a significantly lower preoperative BNP level (median 42, IQR 14;134) compared to persons with HF (median 145, IQR 49;417, p=0.008). The change in BNP levels, pre- and postoperatively, in persons with HF (median 8, IQR 81;193) and without HF (median 18, IQR 9;172) did not differ significantly (p=0.205). Survival duration (in days) was significantly (p<0.001) different between the four groups: low BNP without HF (median 2306, IQR 1866;2724), high BNP without HF (median

1164, IQR 917;1224), low BNP with HF (median 2990, IQR 1193;3362), and high BNP with HF (median 583, IQR 87;790, Figure 2). In the post-hoc pairwise comparisons the difference between 'low BNP without HF' and 'high BNP with HF' remained significant (adjusted p=0.004), and also the difference between 'low BNP with HF' and 'high BNP with HF' (adjusted p=0.008). Survival was shortest in the group with the high BNP levels with HF.

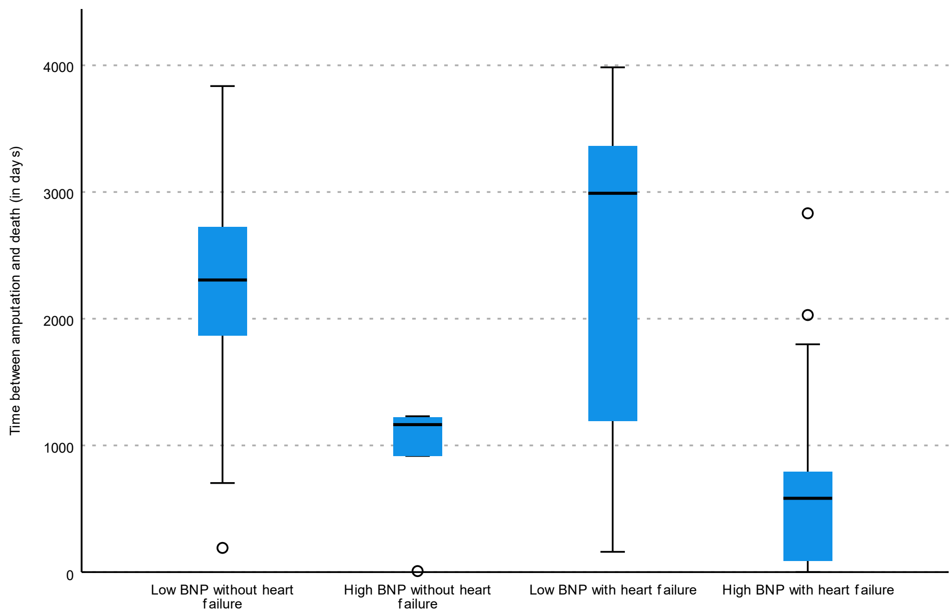

Figure 2: Boxplot Kruskal Wallis Test for BNP level, heart failure and survival. Figure 2 shows a boxplot of brain natriuretic peptide (BNP) levels, heart failure and survival. There were four groups: low BNP without heart failure (n=14), high BNP without heart failure (n=5), low BNP with heart failure (n=9), and high BNP with heart failure (n=18). The statistical analysis revealed a significant difference between the 'low BNP without heart failure' and 'high BNP with heart failure' groups (adjusted p=0.004), as well as between the 'low BNP with heart failure' and 'high BNP with heart failure' groups (adjusted p=0.008). The median is shown by the line within each box, the interquartile range (IQR) by the box itself (25th to 75th percentiles). Outliers: O. BNP refers to brain natriuretic peptide.

Discussion

The results of this study showed that survivors had lower pre- and postoperative BNP levels compared to non-survivors. In addition, individuals with dysvascular mLLA and with preoperative BNP levels ≤91 pg/ml lived 1618 (median) days longer than those with preoperative BNP levels median >91 pg/ml. Our results on preoperative BNP levels are in line with the findings of a pilot study.[16] The preoperative NT-proBNP levels in survivors (n=15) were also lower than in non-survivors (30 days, n=4) in that study, but the difference was not significant.[16] The level of NT-proBNP can also be elevated in kidney failure, because the kidneys do not excrete NT-proBNP properly.[18] In BNP this phenomenon occurs to a lesser extent.[18] Elimination of BNP occurs cellularly by endocytosis and only partially through the kidneys.[7,21]

In a study involving persons undergoing cardiac surgery with cardiopulmonary bypass, no association was found between preoperative BNP levels and mortality but postoperative BNP levels (≥484 pg/mL) were strongly associated with mortality.[22] In contrast, another study found that higher preoperative (NT-pro)BNP values in vascular surgery patients were associated with a higher risk for perioperative cardiovascular complications.[23] Additionally a retrospective cohort study (median follow-up of 7 years) among persons with cardiovascular disease found that mortality rates increased gradually with increasing BNP levels.[24] In a meta-analysis it was suggested determining preoperative (NT-pro)BNP levels may facilitate risk stratification of patients undergoing noncardiac surgery. An elevated BNP level was a powerful predictor of adverse cardiovascular outcomes at 30 days, independent of other conventional risk factors.[25] A recent study supports these findings for both preoperative and postoperative BNP values.[26]

The (NT-pro)BNP is an emerging tool for screening and a guide to start a treatment in subclinical HF.[7] Cardiac disease may be underdiagnosed in persons with a dysvascular mLLA. Limb pain may limit their physical activity below the levels necessary to provoke symptoms of cardiac disease. BNP levels also appear to be elevated in persons with asymptomatic left ventricular systolic dysfunction.[27] A high BNP level may assist physicians in early diagnosing and managing cardiac stress [7] in persons with dysvascular mLLA to prevent complications in the perioperative and rehabilitation phase. People with a mLLA have significantly higher energy cost of walking compared to people without an amputation.[28] High preoperative BNP levels in persons with dysvascular mLLA may indicate the potential presence of a serious ventricular disease, with implications for rehabilitation, particularly when persons begin walking with a prosthesis resulting in additional cardiac strain. This underscores the need for careful cardiac monitoring and management in this population to improve perioperative and rehabilitation outcomes.

Persons without HF had a significantly lower preoperative BNP level compared to persons with HF. Sensitivity of BNP in diagnosing HF is much better than its specificity which means that the test is better at ruling out HF than confirm it.[17] As hypothesized, our results show a significant difference between the group with a low BNP without HF and the group with a high BNP with HF, with a better survival for the group with a low BNP and without HF. These results suggest that the absence of (sub)clinical HF is positively linked with survival duration. Less obvious is the significant difference between the group with low BNP with HF and the group with high BNP with HF. Especially since a low BNP would exclude HF in a large proportion of cases. An expert review study showed that BNP levels are proportional to the severity of HF.[29] Our results showed that there is an interaction effect, where the effect of BNP is the largest. In future study also the possible treatment of HF and its effect should be monitored.

Our results showed no significant difference in change score of pre- and postoperative BNP between survivors and non-survivors. This outcome could be the effect of lack of observations or lack of an association. Arguably, the BNP level may change after amputation, because the part of the leg that is poorly perfused or infected is amputated, which can affect the load and/or stress on the heart. Furthermore, (NT-pro)BNP has a high intraindividual biological variation, which may hamper the interpretation of changes in (NT-pro)BNP levels for the detection of disease progression and their use in (NT-pro)BNP-guided treatment.[30]

The median survival duration for the total group is 1195 days (3.3 years, IQR 1.0;6.3), this is much higher than a mean survival of 273 days (0.75 year) in a previous study.[31] Consequently the 1-year survival of 75% is also higher than the 52%[32] and 56%[33] in other studies or 66% in that study.[31] These differences might be related to the fact that in our study more knee disarticulations were performed, 42%, than in a previous study, 7%, and relatively few transfemoral amputations, 10%, and 47% in that study.[31] Transfemoral amputations are associated with higher perioperative cardiac event rates and higher mortality rates.[3,31,34] Of those undergoing a mLLA, 17% had an ipsilateral reamputation. This is similar to previous studies which reported 9-26% ipsilateral reamputations after a mLLA.[31] These data show that the percentage of complications of the residual limb after amputation in our study is similar to previous studies.

A limitation of this study is the small sample size since BNP levels were not routinely determined in all persons to be amputated at Nij Smellinghe Hospital, possibly limiting generalization of our outcomes. However, compared to a multicenter study in the North of the Netherlands, our population appears to be similar in terms of age (73 years versus 72 years) and gender (male 71% versus 65%).[31] Future research is needed to confirm or refute our results in a larger study population. A prospective multicenter study is expected to provide a larger study sample.

Another limitation is that the timing of the BNP determination was less standardized than anticipated. To test robustness of our outcomes, we reanalyzed our data including only those data when BNP was determined 14 days before and after amputation. In this post-hoc analysis our reported results were confirmed (Appendix 1). Future research should prospectively measure BNP with standardized measurement protocol with BNP measurements both pre- and postoperatively, taken close to the amputation. Additionally, combined measurements of NT-proBNP and BNP (NT-proBNP/BNP ratio)[7] may enhance prognostic accuracy in predicting adverse outcomes among hospitalized patients with HF.[35]

Finally, we were not able to analyze whether persons were treated for HF and whether that treatment affected survival. For future research it would be interesting whether treatment affects outcomes for this population.

Conclusion

The study highlights the importance of BNP as a promising biomarker for cardiac stress and its potential role in predicting survival outcomes in individuals with mLLA. High levels of BNP, also in combination with HF, were predictive for poorer survival in persons with dysvascular mLLA. Elevated BNP levels in persons with a mLLA may indicate the presence of serious ventricular disease, which can complicate rehabilitation due to the increased cardiac strain associated with the higher energy cost of walking post-amputation. Further research is needed to validate these findings and to explore the potential benefits of targeted cardiac management in this population.

Conflict of Interest:

The authors have no conflicts of interest to declare.

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Appendix

Appendix 1: BNP measurements in the total groups, survivors and non-survivors

Variables	Total group	Survivors*	Non-survivors	p-value
Preoperative BNP	n=38	n=11	n=27	
BNP level in pg/ml, median (IQR)	93 (32;201)	42 (20;69)	145 (41;417)	p=0.017
Days before amputation determined, median (IQR)	1 (0;2)	1 (1;2)	1 (0;2)	
Postoperative BNP	n=32	n=5	n=27	
Median level in pg/ml, median (IQR)	145 (30;324)	26 (16;42)	239 (48;343)	p=0.009
Days after amputation determined, median (IQR)	1 (1;5)	1 (1;4)	2 (1;5)	
Change in BNP level (pre-vs postoperative)	n=21	n=4	n=17	
Median change in level in pg/ml, median (IQR)	15 (1;152)	10 (0;19)	17 (1;212)	p=0.370

IQR=interquartile range

* Survival determined at February 17, 2023

Persons without HF had a significantly lower preoperative BNP value (median: 43, IQR 21;135) compared to persons with HF (median 145, IQR 47;423, p=0.05).

The change in BNP levels (pre- and postoperatively) in persons with HF (median 7, -2;161) and without HF (median 16, IQR 9;173) was not significantly different (p=0.573).

Survival duration was significantly (p=0.001) different between the four groups: low BNP without HF, high BNP without HF, low BNP with HF and high BNP with HF. In the post-hoc pairwise comparisons the difference between 'low BNP without HF' and 'high BNP with HF' remained significant (adjusted p=0.007), and also the difference between 'low BNP with HF' and 'high BNP with HF' (adjusted p=0.014).