

# Prognostic value of N-terminal pro-brain natriuretic peptide in elderly people with acute myocardial infarction: prospective observational study

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## ABSTRACT

**Objective** To examine the influence of age on the predictive value of N-terminal pro-brain natriuretic (NT-proBNP) peptide assay in acute myocardial infarction.

**Design** Prospective observational study.

**Setting** All intensive care units in one French region.

**Participants** 3291 consecutive patients admitted for an acute myocardial infarction, from the RICO survey (a French regional survey for acute myocardial infarction).

**Main outcome measure** Cardiovascular death at 1 year.

**Results** Among the 3291 participants, mean age was 68 (SD 14) years and 2356 (72%) were men. In the study population, the median NT-proBNP concentration was 1053 (interquartile range 300-3472) pg/ml. Median values for age quarters 1 to 4 were 367 (119-1050), 696 (201-1950), 1536 (534-4146), and 3774 (1168-9724) pg/ml ( $P<0.001$ ). A multiple linear regression analysis was done to determine the factors associated with the pro-peptide concentrations in the overall population. NT-proBNP was mainly associated with age, left ventricular ejection fraction, creatinine clearance, female sex, hypertension, diabetes, and anterior wall infarction. At one year's follow-up, 384 (12%) patients had died from all causes and 372 (11%) from cardiovascular causes. In multivariate analysis, NT-proBNP remained strongly associated with the outcome, beyond traditional risk factors including creatinine clearance and left ventricular ejection fraction, in each age group except in the youngest one ( $<54$  years) ( $P=0.29$ ). The addition of NT-proBNP significantly improved the performance of the statistical model in the overall study population ( $-2\log$  likelihood 3179.58 v 3099.74,  $P<0.001$ ) and in each age quarter including the upper one (1523.52 v 1495.01,  $P<0.001$ ). The independent discriminative value of NT-proBNP compared with the GRACE score was tested by a diagonal stratification using the median value of the GRACE score and NT-proBNP in older patients (upper quarter). Such stratification strikingly identified a high risk group—patients from the higher NT-proBNP group and with a high risk score—characterised by a risk of death of almost 50% at one year.

**Conclusions** In this large contemporary non-selected cohort of patients with myocardial infarction, NT-proBNP concentration had incremental prognostic value even in the oldest patients, above and beyond the GRACE risk score and traditional biomarkers after acute myocardial infarction. These data further support the potential interest of clinical trials specifically assessing NT-proBNP measurement as a guide to current treatment strategies, as well as novel strategies, in older patients with acute myocardial infarction.

## INTRODUCTION

The number of older people with acute myocardial infarction has increased in the past two decades.<sup>1</sup> Although mortality after myocardial infarction has decreased over time in older patients, it has remained markedly higher than in younger patients.<sup>2</sup> Moreover, although older patients have a much higher rate of comorbidities and are treated less vigorously, age itself has been found to be an independent risk factor after myocardial infarction.<sup>3,4</sup> This emphasises the importance of determining suitable tools for risk stratification in older patients after myocardial infarction.<sup>5</sup> B-type natriuretic peptide (77-108 amino acids) and its N-terminal (1-76 amino acids) counterpart (N-terminal pro-brain natriuretic peptide or NT-proBNP) are secreted from cardiomyocytes in response to increased wall tension.<sup>6,7</sup> Both natriuretic peptides have emerged as major prognostic factors for short term and long term mortality across the whole spectrum of acute coronary syndromes and beyond traditional risk markers.<sup>8,9</sup> Among factors that potentially affect plasma B-type natriuretic peptide, older age and altered left ventricular ejection fraction profoundly increase the circulating concentration.<sup>10-12</sup> B-type natriuretic peptide concentrations have been shown to add to the prognostic information in patients with myocardial infarction and left ventricular dysfunction.<sup>13</sup> However, few studies have examined the prognostic information derived from the B-type natriuretic peptide concentration in older patients.<sup>14</sup>

Using a large non-selected contemporary cohort of patients with acute myocardial infarction, this study aimed to investigate the influence of age on the predictive value for mortality of concentrations of NT-proBNP at admission to hospital.

## METHODS

### Patient population

We recruited the participants in this study from the RICO (observatoire des infarctus de Côte-d'Or) survey, a French regional survey for acute myocardial infarction. Briefly, the population based RICO survey collects in-hospital data from consecutive patients admitted for acute myocardial infarction in all public centres or privately funded hospitals of one eastern region of France.<sup>15</sup> In the study reported here, we included patients admitted to one of the aforementioned centres between 1 January 2001 and 31 December 2006 with acute myocardial infarction within 12 hours after onset of symptoms. Myocardial infarction was diagnosed according to European Society of Cardiology and American College of Cardiology criteria.<sup>16</sup>

### Data collection

We collected data on patients' age, sex, and cardiovascular risk factors (history of hypertension or treated hypertension, known history of diabetes, treated hypercholesterolaemia, body mass index (kg/m<sup>2</sup>), current smoking (reported active smoking of cigarettes within three months before this admission)). We defined previous myocardial infarction as at least one myocardial infarction before the admission. We also collected data on haemodynamic parameters at admission (heart rate, systolic and diastolic blood pressure) and Killip class: Killip 1—no clinical signs of heart failure, Killip 2—heart failure (rales in lungs (up to 50% of lung fields), S3 gallop, or elevated jugular venous pressure consistent with heart failure), Killip 3—severe heart failure (pulmonary oedema with rales in >50% of lung fields), Killip 4—cardiogenic shock. Patients were diagnosed as having ST segment elevation myocardial infarction when they had new or presumed new ST segment elevation greater than 1 mm seen in any location or new left bundle branch block on the index or subsequent electrocardiogram. Left ventricular ejection fraction was measured by echocardiography at day 3±1 after admission with the Simpson method and dichotomised at 40% for greater clinical relevance.

We calculated the Global Registry of Acute Coronary Events (GRACE) risk score with admission variables including age, heart rate, serum creatinine, systolic blood pressure, Killip class, cardiac arrest, ST segment deviation, and cardiac markers ([www.outcomes-umassmed.org/grace/acs\\_risk.cfm](http://www.outcomes-umassmed.org/grace/acs_risk.cfm)).<sup>17</sup> The GRACE risk model has shown excellent characteristics as a predictor of mortality, providing most (>90%) of the prognostic information. We obtained information on cardiovascular mortality at one year's follow-up (mean 310 (SD 113) days) by telephone interview or mail from the patient, the patient's relatives, or the

treating physician. One year of follow-up was achieved in 3225 (98%) patients. Each patient gave written consent before participation.

### Laboratory analysis

Blood samples for measurement of concentrations of NT-proBNP, C reactive protein, and creatinine were collected on admission in tubes containing EDTA. Median time from onset of symptoms to blood sampling was 160 (interquartile range 85–466) minutes. We determined plasma NT-proBNP concentrations by electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics). The inter-assay and intra-assay coefficients of variation were both less than 3.1%. The sensitivity of the assay was 0.6 pmol/l. The cross reactivity with other natriuretic peptides (B-type natriuretic peptide, atrial natriuretic peptide, and C-type natriuretic peptide) was <0.01%. We measured C reactive protein with a dimension Xpand (Dade Behring, Newark, NE) and creatinine with a Vitros 950 analyser (Ortho Clinical Diagnostics, Rochester, NY). We used the Cockcroft-Gault formula to estimate serum creatinine clearance.<sup>18</sup> We assessed peak plasma troponin Ic by sampling every eight hours during the first two days after admission (Dimension Vista Intelligent Lab System, Siemens).

### Statistical analysis

We divided the patients into quarters on the basis of their age. We used the  $\chi^2$  test for trend to compare categorical variables across the quarters. For continuous variables, we used the Kolmogorov-Smirnov test to check the normality of the distribution and compared the variables by either one way analysis of variance or Kruskal-Wallis one way analysis, as appropriate. We did a multiple linear regression analysis to determine the factors that were associated with the pro-peptide concentrations. Variables that were significantly associated in univariate analysis were introduced as covariates in the multiple regression model. Before doing the multivariable linear regression analysis, we tested the nature of the relation with log NT-proBNP with and without log transformation of each non-normally distributed variable. We chose the expression of the data (log transformed or not) that gave the best fitting of linearity for introduction into the model. Left ventricular ejection fraction was log transformed.

We used multivariate Cox regression analysis to identify independent predictors of cardiovascular mortality at one year. We tested all the variables listed in table 1 in univariate analysis and introduced them into the multivariate model if the P value was <0.10. Variables associated with the prognosis were sex, age, hypertension, previous myocardial infarction, left ventricular ejection fraction <40%, Killip class >1, C reactive protein >3 mg/l, peak troponin >100 upper limit of normal, heart rate, creatinine clearance <30 ml/min, diabetes mellitus, and GRACE risk score. We included these as covariates in the multivariate analysis, either without or with NT-proBNP, adjusted for sex, previous myocardial infarction, left ventricular ejection fraction

**Table 1** | Characteristics of study population divided by age. Values are numbers (percentages) unless stated otherwise

Characteristics	Quarter (age)				P value
	1 (n=822)	2 (n=823)	3 (n=823)	4 (n=823)	
Age (years):					
Median	47	61	73	82	
Interquartile range	43-51	57-64	70-75	79-85	
Range	20-54	54-68	68-77	77-103	
Male	693 (84)	676 (82)	559 (68)	428 (52)	0.001
Hypertension	241 (29)	421 (51)	525 (64)	561 (68)	0.001
Diabetes	76 (9)	177 (22)	231 (28)	259 (31)	0.001
Dyslipidaemia	350 (42)	425 (52)	402 (49)	305 (37)	0.001
Current smoker	559 (68)	272 (33)	89 (11)	36 (4)	0.001
Previous myocardial infarction	61 (7)	101 (12)	117 (14)	163 (20)	0.001
Median (interquartile range) body mass index (kg/m <sup>2</sup> )	26 (24-30)	27 (24-30)	27 (24-29)	25 (23-28)	0.001
ST segment elevation myocardial infarction	529 (64)	483 (59)	452 (55)	458 (56)	0.001
Anterior wall location	316 (38)	305 (37)	314 (38)	271 (33)	0.075
Median (interquartile range) creatinine clearance (ml/min)	108 (88-126)	87 (71-105)	63 (50-76)	44 (33-57)	0.001
Median (interquartile range) NT-proBNP (pg/ml)	367 (119-1050)	696 (201-1950)	1536 (534-4146)	3774 (1168-9724)	0.001
Median (interquartile range) C reactive protein (mg/l)	4.66 (2-11)	6.3 (2.4-18.5)	6.8 (2.5-23)	10.7 (3.6-39.9)	0.001
Median (interquartile range) heart rate (beat/min)	76 (65-88)	76 (65-90)	78 (66-91)	80 (67-94)	0.001
Killip class >1	110 (13)	173 (21)	292 (35)	414 (50)	0.001
Median (interquartile range) LVEF (%)	59 (50-65)	55 (45-63)	52 (42-63)	48 (38-57)	0.001
Median (interquartile range) GRACE score	107 (89-126)	129 (108-147)	154 (133-174)	171 (150-196)	<0.001
Troponin >100 upper limit of normal	516 (63)	491 (60)	470 (57)	474 (58)	0.086
Cardiac arrest	64 (8)	49 (6)	41 (5)	32 (4)	0.005

GRACE=Global Registry of Acute Coronary Events; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal proB-type natriuretic peptide.

<40%, C reactive protein >3 mg/l, diabetes, peak troponin >100 upper limit of normal, and GRACE score (table 2). As age is a potential confounder of the relation between NT-proBNP and outcome, we tested its interaction in univariate analysis and as a covariate in multivariate analysis. The goodness of the fit was tested by the -2log likelihood  $\chi^2$  criterion. We tested the additional prognostic information from NT-proBNP in each quarter by comparing the -2log likelihoods of the model. We used the SPSS 13.0 software package for all analyses.

## RESULTS

Among the 3291 participants, the mean age was 68 (SD 14) years and 2356 (72%) were men. Table 1 lists the

baseline characteristics categorised by age quarters. In the study population, the median NT-proBNP concentration was 1053 (interquartile range 300-3472) pg/ml. Median values in quarters 1 to 4 were 367 (119-1050), 696 (201-1950), 1536 (534-4146), and 3774 (1168-9724) pg/ml ( $P<0.001$ ). Multiple linear regression analysis showed that NT-proBNP concentration was mainly associated with age ( $\beta=0.010$ ,  $P<0.001$ ), left ventricular ejection fraction ( $\beta=-1.628$ ,  $P<0.001$ ), creatinine clearance ( $\beta=-0.939$ ,  $P<0.001$ ), female sex ( $\beta=0.151$ ,  $P<0.001$ ), hypertension ( $\beta=0.104$ ,  $P<0.001$ ), diabetes ( $\beta=0.062$ ,  $P=0.031$ ), and anterior wall infarction ( $\beta=0.089$ ,  $P<0.001$ ).

At one year's follow-up, 384 (12%) patients had died from all causes and 372 (11%) from cardiovascular

**Table 2** | Predictor of one year cardiovascular mortality by Cox regression analysis

Quarter (age)	Cardiovascular death—No (%)	Unadjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value
Overall	372/3291 (11.3)	2.55 (1.99 to 3.26)	<0.001	2.82 (2.22 to 3.59)	<0.001
Q1	25/822 (3.0)	1.77 (0.61 to 5.13)	0.29	1.45 (0.52 to 3.88)	0.50
Q2	45/823 (5.5)	5.11 (2.42 to 10.81)	<0.001	4.52 (2.05 to 9.98)	<0.001
Q3	103/823 (12.5)	2.53 (1.61 to 3.98)	<0.001	1.92 (1.24 to 2.98)	0.003
Q4	199/823 (24.2)	2.34 (1.66 to 3.29)	<0.001	2.55 (1.79 to 3.64)	<0.001

Adjusted for sex, previous myocardial infarction, left ventricular ejection fraction <40%, C reactive protein >3 mg/l, diabetes, peak troponin, and GRACE (Global Registry of Acute Coronary Events) score.

causes. Univariate and multivariate analysis showed that the level of risk in older patients derived from the concentration of NT-proBNP was very similar to that found in the overall population (hazard ratio 2.34 *v* 2.55) (table 2). In multivariate analysis, NT-proBNP remained strongly associated with the outcome, beyond traditional risk factors including creatinine clearance and left ventricular ejection fraction, in each age group except the youngest one (<54 years) ( $P=0.29$ ). Moreover, addition of NT-proBNP significantly improved the performance of the statistical model in the overall study population ( $-2\log$  likelihood 3179.58 *v* 3099.74,  $P<0.001$ ) and in each quarter including the upper one (1523.52 *v* 1495.01,  $P<0.001$ ). To further investigate the independent discriminative value of NT-proBNP compared with the GRACE score, we did a diagonal stratification using the median value of the GRACE score and NT-proBNP in older patients (upper quarter) (figure). Such stratification strikingly identified a high risk group—patients from the higher NT-proBNP group and with a high risk score—which was characterised by a risk of death of almost 50% at one year (figure). We found no significant interaction between age and NT-proBNP for the outcome in any age categories.

## DISCUSSION

Major randomised and observational studies have provided consistent observations that concentrations of B-type natriuretic peptide or NT-proBNP are useful tools for risk stratification of patients with acute myocardial infarction, particularly for predicting mortality.<sup>8 9 18-22</sup> These peptides have a powerful prognostic value both in patients without a history of heart failure and in those without clinical signs of left ventricular dysfunction on admission or during the hospital stay. Galvani et al's meta-analysis showed that the prognostic value of natriuretic peptides is similar for short term and long term prediction, when peptides were measured at the first contact with the patient or during the hospital stay, for B-type natriuretic peptide or NT-proBNP, and in patients with ST segment elevation

myocardial infarction or non-ST segment elevation myocardial infarction.<sup>23</sup> However, none of these studies specifically assessed the predictive value of the natriuretic peptide in elderly people and some even excluded older patients.<sup>9</sup> In the light of the increasing prevalence of acute myocardial infarction and the increasing age of patients, understanding the relation between age and NT-proBNP concentrations is a key factor in the successful stratification of risk in acute myocardial infarction. This is one of the first studies to specifically assess the prognostic value of NT-proBNP in older patients with myocardial infarction.

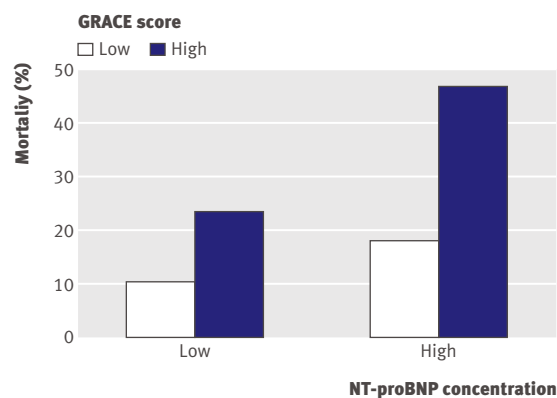
### Increased NT-proBNP and older people

A striking increase in mean and upper centile values for NT-proBNP with age has been reported in healthy volunteers.<sup>24 25</sup> After multivariate adjustment, a 10 year increase in age was associated with a 1.4-fold increase in pro-peptide concentration.<sup>24</sup> In animal studies, an increase in natriuretic peptide gene expression has been documented with advancing age.<sup>26</sup> Furthermore, the increase in natriuretic peptide concentrations with age may reflect a higher prevalence of subclinical cardiac disease in healthy older people. Our study shows that sex, renal function, and left ventricular ejection fraction are the major contributors to elevated concentrations of the pro-peptide in patients with acute myocardial infarction. Our data also suggest that comorbidities such as diabetes and hypertension have little impact on NT-proBNP in older people with myocardial infarction.

Secretion of natriuretic peptides is markedly regulated by wall tension of the left ventricles,<sup>27</sup> and B-type natriuretic peptide concentrations are indicators of left ventricular systolic function after myocardial infarction.<sup>28</sup> The mechanisms whereby sex and renal function influence circulating concentrations of NT-proBNP remain unclear. Clinical studies have reported a decrease in the clearance of natriuretic peptides from plasma in older patients, even in the absence of renal dysfunction.<sup>29</sup> Impairment of non-renal clearance mechanisms, such as platelet associated clearance receptors, may contribute to the higher concentrations seen in older people.<sup>30</sup> The proportion of women was higher in the upper age quarter in our study, and the proportion of women had an independent impact on pro-peptide concentrations whatever the age group. The physiological basis for this sex related difference is unclear. A stimulatory effect of female sex hormones has been reported in experimental studies,<sup>31</sup> and production of B-type natriuretic peptide may be sensitive to oestrogen regulation.<sup>32</sup>

### NT-proBNP and mortality

Our data from patients in routine clinical practice show that the concentration of NT-proBNP on admission remains a useful tool for risk stratification, even in older patients. Few data are available on the prognostic value of NT-proBNP in elderly patients with acute myocardial infarction. Drewniak et al, in a small study specifically investigating older patients (>



One year cardiovascular mortality according to concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and Global Registry of Acute Coronary Event (GRACE) risk score in the oldest patients (upper quarter)



## WHAT IS ALREADY KNOWN ON THIS TOPIC

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of long term mortality in patients with acute coronary syndrome

## WHAT THIS STUDY ADDS

Despite increased concentrations in older patients with acute myocardial infarction, NT-proBNP retained its prognostic capacity and correlated significantly with one year cardiovascular mortality

NT-proBNP concentration provides prognostic data above and beyond that provided by major predictors such as the GRACE risk score and traditional biomarkers

65 years), included 161 patients with acute myocardial infarction. NT-proBNP concentrations were measured within the first 48 hours of admission to hospital, as well as left ventricular ejection fraction, Killip class, and a six minute walk test. The authors found a strong relation between NT-proBNP concentrations and clinical outcomes at six months in such patients.<sup>14</sup> Multivariate analysis showed that age and NT-proBNP were independent predictors of six month mortality. However, confounding factors such as creatinine clearance, history of myocardial infarction, troponins, and the GRACE score were not included as covariates in the multivariate analysis.

Despite a dramatic increase (by a factor of two) in the risk of death, our study based on a large population supports the concept that NT-proBNP in older people (>77 years) retains the same prognostic capacity as in younger patients. In multivariate analysis, NT-proBNP concentration was independently associated with mortality, with a hazard ratio above two in each age group except in younger patients (<54 years). However, the small number of deaths (n=25) in this age group may have resulted in insufficient statistical power. Further studies in a larger population are needed to quantify the predictive value of NT-proBNP in young patients with myocardial infarction. NT-proBNP has incremental prognostic value in older patients, beyond traditional risk markers such as troponin, GRACE score, C reactive protein, left ventricular ejection fraction, diabetes, and renal function, and even in the presence of high levels of the pro-peptide. To the best of our knowledge, only one study has analysed the complementary predictive value of B-type natriuretic peptide and GRACE score in patients admitted to the emergency department for chest pain suggestive of acute coronary syndrome.<sup>33</sup> In this study, high troponin concentration did not predict outcomes. These data are consistent with our findings showing the lack of an independent predictive value of troponin.

The high incidence of myocardial infarction and increased mortality in the elderly population has identified this age group as one in which effective acute treatment strategies would have the greatest potential impact in achieving a reduction in mortality. Our findings clearly indicate that a single NT-proBNP measurement in the early hours after admission would be helpful in defining risk in older patients. Despite increased concentrations of NT-proBNP in older

patients with acute myocardial infarction, NT-proBNP retained its prognostic capacity and correlated significantly with one year cardiovascular mortality.

## Study limitations

A limitation of this study is that the population of the RICO survey is almost exclusively white, and thus we were unable to investigate the influence of ethnicity on NT-proBNP. Given the strength of the findings, adjustment for these factors would be unlikely to change the main conclusion of our work. However, the cut-off points determined from this study may not be applicable in other community cohorts.

## Conclusions

In this large contemporary non-selected cohort of patients with myocardial infarction, we have shown for the first time that NT-proBNP concentration has incremental prognostic value even in older patients, above and beyond GRACE risk score and traditional biomarkers after acute myocardial infarction. Inspired by the use of B-type natriuretic peptides in the management of heart failure,<sup>34</sup> a very important question is now emerging as to whether B-type natriuretic peptide concentrations should influence management of patients with acute myocardial infarction.<sup>35</sup> The rapid and accurate assessment of risk is crucial for effective management of such patients. Moreover, patients at high risk, such as elderly people, may derive maximal benefit from an early aggressive treatment strategy.<sup>22</sup> Among the developed risk scores, the GRACE risk score, driving more than 90% of the prognostic information, is currently considered to be the best risk score in acute coronary syndromes. However, prospective studies specifically assessing the incremental value, beyond GRACE risk score, of biomarkers such as NT-proBNP are urgently needed.<sup>36</sup> In this context, our data further support the potential interest of clinical trials specifically investigating NT-proBNP measurement as a guide to current treatment strategies, as well as novel strategies, in older patients with acute myocardial infarction.

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**Contributors:** MZ, JCB, LL, and YC were involved in conception and design. GD, PS, PB, IL'H, MV-M, HM, and PG drafted the manuscript or revised it critically for important intellectual content. LL and MZ analysed and interpreted the data. YC is the guarantor.

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**Competing interests:** None declared.

**Ethical approval:** This study was approved by the ethics committee of the University Hospital of Dijon, and each patient gave written consent before participation.

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