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 (−2log 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. Although mortality after myocardial infarction has decreased over time in older patients, it has remained markedly higher than in younger patients. 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. This emphasises the importance of determining suitable tools for risk stratification in older patients after myocardial infarction. 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. 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. Among factors that potentially affect plasma B-type natriuretic peptide, older age and altered left ventricular ejection fraction profoundly increase the circulating concentration. Both B-type natriuretic peptide concentrations have been shown to add to the prognostic information in patients with myocardial infarction and left ventricular dysfunction. However, few studies have examined the prognostic information derived from the B-type natriuretic peptide concentration in older patients.
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. 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.

**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/m²], 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). 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 (Elecys 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 Vittos 950 analyser (Ortho Clinical Diagnostics, Rochester, NY). We used the Cockcroft-Gault formula to estimate serum creatinine clearance.14 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 χ² 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...
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 $-2\log\ likelihood$ $\chi^2$ criterion. We tested the additional prognostic information from NT-proBNP in each quarter by comparing the $-2\log\ likelihood$ 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 1 | Characteristics of study population divided by age. Values are numbers (percentages) unless stated otherwise

| Characteristics                        | 1 (n=822) | 2 (n=823) | 3 (n=823) | 4 (n=823) | P value |
|----------------------------------------|-----------|-----------|-----------|-----------|---------|
| 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/m²) | 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 (88-124) | 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 (45-65) | 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 pro-B-type natriuretic peptide.

### 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 NT-proBNP compared with the GRACE score, we did a diagonal stratification using the median value of NT-proBNP compared with the GRACE score 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.\(^8\)\(^9\)\(^18\)\(^22\)

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.\(^21\) However, none of these studies specifically assessed the predictive value of the natriuretic peptide in elderly people and some even excluded older patients.\(^3\) 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.\(^24\)\(^25\) After multivariate adjustment, a 10 year increase in age was associated with a 1.4 fold increase in pro-peptide concentration.\(^24\) In animal studies, an increase in natriuretic peptide gene expression has been documented with advancing age.\(^26\)\(^27\) 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,\(^27\) and B-type natriuretic peptide concentrations are indicators of left ventricular systolic function after myocardial infarction.\(^28\) 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.\(^29\) Impairment of non-renal clearance mechanisms, such as platelet associated clearance receptors, may contribute to the higher concentrations seen in older people.\(^30\) 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,\(^31\) and production of B-type natriuretic peptide may be sensitive to oestrogen regulation.\(^32\)

**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 (\(>55\) years), documented an increase in the concentration of the pro-peptide. Our data show that a 10 year increase in age is associated with a 1.4 fold increase in NT-proBNP concentration.
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

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, a very important question is now emerging as to whether B-type natriuretic peptide concentrations should influence management of patients with acute myocardial infarction. 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. 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. 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.

Conclusions

We thank Anne Cécile Lagrost and Juliane Berchoud for assistance with the research and Philip Bastable for assistance with English.

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.

Funding: This work was supported by the University Hospital of Dijon and the Association de Cardiologie de Bourgogne and by grants from the Union Régionale des Caisses d’Assurance Maladie de Bourgogne and the Agence Régionale d’Hospitalisation de Bourgogne.

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.

1 Masoudi FA, Foody JM, Havranek EP, Wang Y, Radford MJ, Allman RM, et al. Trends in acute myocardial infarction in 4 US states between 1992 and 2001: clinical characteristics, quality of care, and outcomes. Circulation 2006;114:2806-14.

2 Tahir SM, Price LL, Shah PB, Welt FG. Eighteen year (1985-2002) analysis of incidence, mortality, and cardiac procedure outcomes of acute myocardial infarction in patients > or = years of age. Am J Cardiol 2008;101:930-6.
Batchelor WB, Anstrom KJ, Muhlbaiher LH, Gosswald R, Weintraub WS, O'Neill WW, et al. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. *J Am Coll Cardiol* 2000;36:723-30.

Basak K, Wilkinson P, Deaner A, Fluck D, Ranjadayan K, Timmis A. How should age affect management of acute myocardial infarction? A prospective cohort study. *Lancet* 1999;353:955-9.

Pearte CA, Furberg CD, O'Meara ES, Psaty BM, Kuller L, Powe NR, et al. Characteristics and baseline clinical predictors of future fatal versus nonfatal coronary heart disease events in older adults: the cardiovascular health study. *Circulation* 2006;113:2177-85.

Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;339:321-28.

Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL Jr. Biology of the natriuretic peptides. *Am J Cardiol* 2008;101:3-8.

De Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;345:1014-21.

Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002;106:2913-8.

Davis KM, Fish LC, Minaker KL, Elahi D. Atrial natriuretic peptide levels in the elderly: differentiating normal aging changes from disease. *J Gerontol A Biol Sci Med* 1996;51:M95-101.

Luchner A, Burnett JC Jr, Jougasaki M, Hense HW, Held IM, Maders F, et al. Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. *J Hypertens* 2000;18:1121-8.

Sayama H, Nakamura Y, Saito N, Kinosita M. Why is the concentration of plasma brain natriuretic peptide in elderly patients greater than normal? *Coron Artery Dis* 1999;10:537-40.

Richards AM, Nicholls MG, Espiner E, Lainchbury JG, Troughton RW, Elliott J, et al. B-type natriuretic peptides and ejection fraction for stratification of patients with acute coronary syndromes. *Circulation* 2003;107:278-92.

Drewniak W, Snepec G, Zaukiewicz M, Bons M, Dąbrowski M. Prognostic value of the N-terminal pro-B-type natriuretic peptide in the elderly with acute myocardial infarction. *Kardiol Pol* 2008;66:750-5.

Vergès B, Zeller M, Beer JC, Cottin Y, RICO Survey Working Group. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) level and prognosis after myocardial infarction in diabetes. *Diabetes Metab* 2008;34(suppl 1):S10-5.

Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.

Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, van der Worp F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;333:1091.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

Omland T, de Lemos JA, Morrow DA, Antman EM, Cannon CP, Hall C, et al. Prognostic value of N-terminal pro-atrial and pro-brain natriuretic peptide in patients with acute coronary syndromes. *Am J Cardiol* 2002;89:463-5.

James SK, Lindahl B, Siegbahn B, Stridsberg M, Venge P, Armstrong P, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;108:275-81.

Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro-brain natriuretic peptide on admission for early risk stratification of non-fatal coronary heart disease events in older adults: the cardiovascular health study. *Circulation* 2006;113:2177-85.

Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;339:321-28.

Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL Jr. Biology of the natriuretic peptides. *Am J Cardiol* 2008;101:3-8.