High plasma N-terminal pro-brain natriuretic peptide level found in diabetic patients after myocardial infarction is associated with an increased risk of in-hospital mortality and cardiogenic shock

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Aims No studies have yet been conducted concerning plasma N-terminal pro-brain natriuretic peptide (Nt-pro-BNP) levels after Myocardial Infarction (MI) and their relationship with short-term outcomes in diabetic patients.

Methods and results Five hundred and sixty patients hospitalized for MI from the RICO survey, including 199 diabetic and 361 non-diabetic subjects, were included in the study. Plasma Nt-pro-BNP levels were measured on admission. Median Nt-pro-BNP levels were significantly higher in diabetic patients compared with non-diabetic patients [245 (81–77) vs. 130 (49–199) pmol/L, P < 0.0001]. This difference remained highly significant after adjustment for age, female gender, creatinine clearance, left ventricular ejection fraction (LVEF), plasma peak troponin, anterior wall necrosis, and hypertension. In multivariable analysis, Nt-pro-BNP levels were negatively associated with creatinine clearance (P < 0.0001) and LVEF (P < 0.0001) and positively associated with plasma peak troponin (P < 0.0001), age (P = 0.0029), diabetes (P = 0.0031), and female gender (P = 0.0102). Diabetic patients showed a 4.7-fold increase in hospital mortality (15.6 vs. 3.3%, P < 0.0001) and a 2.2-fold increase in cardiogenic shock (17.6 vs. 7.7%, P = 0.0004). In multivariable analysis, diabetes was an independent factor for mortality [OR: 1.79 (1.45–2.20); P = 0.0064] and cardiogenic shock [OR: 1.45 (1.22–1.72); P = 0.0364] when the variable Nt-pro-BNP was not introduced into the model, but was less significantly associated with mortality [OR: 1.73 (1.39–2.16); P = 0.0107] and no longer associated with cardiogenic shock when Nt-pro-BNP was in the model.

Conclusion After MI, diabetes is independently associated with high plasma Nt-pro-BNP levels. This elevated Nt-pro-BNP is strongly associated with the increased incidence of in-hospital mortality and cardiogenic shock observed in diabetes. Our findings clearly indicate that plasma Nt-pro-BNP provides highly valuable prognostic information on in-hospital outcome after MI, in particular in diabetic patients.

Introduction

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (Nt-pro-BNP) are secreted from cardiomyocytes in response to increased wall stress.1-4 BNP is produced as a 108 amino acid pro-hormone, pro-BNP, which is enzymatically cleaved into the 32 amino acid BNP and the N-terminal part of the pro-hormone, Nt-pro-BNP.5 Levels of BNP and Nt-pro-BNP correlate with left ventricular dilatation, remodelling, and dysfunction in patients after acute myocardial infarction (MI).5,6 In patients with acute MI, the increase in Nt-pro-BNP is greater than the increase in BNP7 and has a higher discriminative value for early cardiac dysfunction than BNP, suggesting that it may be a more sensitive marker of left ventricular dysfunction.8,9 Plasma Nt-pro-BNP level has been shown to provide valuable prognostic information on short- and long-term mortality in patients with acute MI.5,10

KEYWORDS
Diabetes; Myocardial infarction; Nt-pro-BNP; BNP; Ischaemia

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Patients with diabetes mellitus have an increased risk of cardiovascular morbidity and mortality. After MI, diabetic patients have a significantly higher risk of heart failure and cardiogenic shock and therefore a worse outcome, in both short- and long-term. In a recent cross-sectional study, it has been shown that median plasma Nt-pro-BNP is increased in diabetic patients without overt cardiovascular disease, suggesting a higher prevalence of asymptomatic left ventricular dysfunction. However, so far, no data are available on either Nt-pro-BNP levels in diabetic patients after MI, including both ST-elevation and non-ST-elevation MI, or their relationship with short-term outcomes. Thus the aim of our present study was to compare plasma Nt-pro-BNP levels in a large population of diabetic vs. non-diabetic patients hospitalized for acute MI and to examine the relationship between plasma Nt-pro-BNP levels and the incidence of in-hospital cardiac events, including death and cardiogenic shock.

Methods

Patients

From 1 January 2001 to 31 July 2003, the French regional RICO survey prospectively collected in-hospital data from patients hospitalized for acute MI in all public centres or privately funded hospitals of one eastern region of France. All patients with acute MI (symptom onset <24 h before admission), diagnosed according to ESC and ACC criteria, were included in the study. MI was defined by an increase in serum troponin I [10] upper limit of the hospital normal (ULN) range] associated with symptoms of ischaemia and/or characteristic ECG signs. ST segment elevation myocardial infarction (STEMI) was diagnosed when new ST segment elevation >1 mm was seen in any location or when new left bundle branch block was found on the qualifying ECG. During the study period, 560 patients who fulfilled the MI criteria were included. The present study complied with the Declaration of Helsinki and was approved by the Ethics Committee of University Hospital of Dijon. Each patient gave written consent before participation.

Data collection

Demographic data, cardiovascular risk factors, and history were collected. On admission, haemodynamic parameters were recorded (heart rate, systolic and diastolic blood pressures) as well as presence of heart failure defined by a Killip class >1. Treatment variables were also analysed: coronary artery bypass graft (CABG) and primary percutaneous coronary intervention (PCI) defined by a PCI performed <24 h after symptom onset. Left ventricular ejection fraction (LVEF) was measured by echocardiography at 3 ± 1 day after admission using the Simpson method. In-hospital adverse events [death, ventricular arrhythmia: ventricular tachycardia (VT) or fibrillation (VF)], recurrent MI, or cardiogenic shock were recorded. VT was defined by the occurrence of a series of three or more consecutive abnormally shaped premature ventricular complexes whose duration exceeds 120 ms with the ST-T vector pointing opposite the major QRS deflection. VF was defined by the presence of irregular undulations of varying contour and amplitude, without possible distinction of QRS complexes, ST segment or T waves. Cardiogenic shock was defined as systolic blood pressure <90 mmHg persisting for >1 h despite fluid challenge, associated with clinical signs of hypoperfusion. Recurrent MI was assessed on ECG modifications and increased serum troponin.

Laboratory analysis

Blood samples for Nt-pro-BNP level assessment were collected in EDTA containing tubes on admission and stored at −20°C before analysis (<3 days). Plasma Nt-pro-BNP was determined by ELISA using Elecsys Nt-pro-BNP sandwich immunoassay on Elecsys 2010 (Roche Diagnostics). The inter- and intra-assay coefficients of variation were both <3.1%. The sensitivity of the assay was found to be 0.6 pmol/L. The cross-reactivity with other natriuretic peptides [Nt-pro-BNP, atrial natriuretic peptide (ANP), and C-type natriuretic peptide (CNP)] was <0.01%. Baseline serum creatinine clearance was estimated by the Cockcroft-Gault formula. Fasting blood samples were taken on the morning after admission to determine HbA1c and blood lipids. Blood samples for troponin I and creatine kinase-MB (CK-MB) assessment were taken every 8 h during the first 3 days after admission. The peak value of troponin and CK-MB during the hospital stay was also collected. Fasting blood glucose before discharge was also ascertained on days 4 and 5 to evaluate the glycometabolic state for each patient.

Group definition and analysis

Diabetes mellitus was defined according to the ADA definition. We classified patients as having diabetes mellitus if they had a history of diagnosed diabetes or if their mean fasting blood glucose was ≥7.0 mmol/L (126 mg/L) on days 4 and 5 after hospital admission.

Statistical analysis

For continuous variables, a Kolmogorov-Smirnov analysis was performed to test for normality. Continuous data were expressed as median and interquartile range values when non-normally distributed and as mean ± standard deviation when normally distributed. Comparisons of continuous variables between diabetic and non-diabetic patients were performed either by unpaired Student’s t-test for normally distributed data or by non-parametric Mann-Whitney U test for non-normally distributed data. Analysis of covariance was used to compare plasma Nt-pro-BNP mean values between diabetic and non-diabetic patients after adjustment for potential confounding variables (age, gender, creatinine clearance, LVEF, plasma peak troponin, anterior wall necrosis, and hypertension). These variables were chosen because they were significantly associated (P < 0.05) with plasma Nt-pro-BNP levels in univariate analysis. Qualitative data expressed as per cent were compared by χ² test. LVEF was dichotomized at 40% for more clinical relevance. The correlation coefficients (r) were determined by linear regression analysis. Statistical significance of the correlation coefficients was determined by the method of Fisher and Yates. A multivariable linear regression analysis was performed to analyse the influence of different factors on plasma Nt-pro-BNP level. The variables introduced into the model were those that were associated with Nt-pro-BNP with a P < 0.20 in the univariate analysis. These variables were creatinine clearance, plasma peak troponin, LVEF, age, gender, diabetes, hypertension, anterior wall necrosis, and STEMI. Before performing the multivariable linear regression analysis, we tested, for each non-normally distributed variable, the nature of the relationship with plasma Nt-pro-BNP with and without log-transformation of the variable. The expression of the data (log-transformed or not) giving the best fitting of linearity was chosen to be introduced into the model. Thus, LVEF, creatinine clearance, plasma peak troponin, and mean fasting blood glucose were log transformed whereas age was not.

A multivariable logistic regression analysis was performed to identify the factors influencing the in-hospital events (in-hospital death, cardiogenic shock). We entered into a full model all the variables associated with the outcome (death or cardiogenic shock) with a P < 0.20 in univariate analysis. The variables tested by univariate analysis were baseline characteristics with a known relationship with in-hospital outcomes. Before performing the multivariable logistic regression analysis, we tested for each non-normally...
distributed variable the nature of the relationship with the endpoint with and without log-transformation of the variable. The expression of the data (log-transformed or not) giving the best fit of the model was chosen. Thus, only heart rate at admission was log-transformed. 

\( P < 0.05 \) was considered statistically significant and two-sided tests were used. Statistical analyses were performed using the SPSS software (SPSS, Inc, Chicago, IL, USA).

**Results**

**Characteristics of the population**

Over the inclusion period, 683 patients were eligible for the study, of whom 123 were not included because of either unconfirmed diagnosis of MI \((n = 104)\) or absence of written consent by the patient \((n = 19)\). Thus, 560 patients fulfilled the inclusion criteria, of whom 199 (35%) were diabetic, 126 (22%) had previously known diabetes, and 73 (13%) had newly diagnosed diabetes at the time of MI. The median time delay (interquartile range) from symptom onset to hospital admission was 169 (90–360) min. The main clinical and biological characteristics of diabetic and non-diabetic patients are shown in Table 1. Diabetic patients were significantly older and had significantly more hypertension and higher body mass index (BMI) than non-diabetic patients (Table 1). A history of MI or of peripheral arterial disease was more frequent in diabetic subjects, whereas current smoking was more frequent among non-diabetic patients. Revascularization procedures (CABG and primary PCI) were similar for both groups. On admission, heart rate as well as rate of heart failure as defined by Killip class >1 was significantly higher in diabetic patients. As expected, fasting blood glucose and HbA1c were significantly higher in diabetic patients. LVEF values were significantly lower in diabetic patients compared with non-diabetic subjects. All the studied patients had elevated plasma peak troponin levels corresponding to the MI definition. Among the diabetic patients, 95% had an elevated CK-MB level (above the upper limit of the normal range). Among the non-diabetic patients, 94% had an elevated CK-MB level (above the upper limit of the normal range). There was no difference between the two groups with regard to plasma CK-MB or peak plasma troponin, anterior wall MI, or STEMI (Table 1).

**Nt-pro-BNP plasma levels**

As shown in Figure 1, Nt-pro-BNP levels were significantly higher in diabetic patients compared with non-diabetic patients \([245 (81–77) \text{ vs. } 130 (49–199) \text{ pmol/L, } P < 0.0001]\). Plasma Nt-pro-BNP was significantly increased in women (vs. men) \([244 (107–660) \text{ vs. } 130 (49–346) \text{ pmol/L, } P < 0.0001]\), in patients with anterior wall necrosis \([174 (65–549) \text{ vs. } 136 (54–353) \text{ pmol/L, } P = 0.022]\), and in patients with hypertension \([181 (70–484) \text{ vs. } 122 (45–342) \text{ pmol/L, } P = 0.0008]\).

Plasma Nt-pro-BNP was positively correlated with age \((r = 0.31, P < 0.0001)\), fasting glycaemia \((r = 0.13, P = 0.002)\), plasma peak troponin level \((r = 0.11, P = 0.009)\) and negatively correlated with creatinine clearance \((r = -0.38, P < 0.0001)\) and LVEF \((r = -0.31, P < 0.0001)\). No significant correlation was found between plasma Nt-pro-BNP on the one hand and triglycerides, HDL-cholesterol, or LDL-cholesterol on the other.

The difference between diabetic and non-diabetic patients remained highly significant \((P = 0.006)\) after adjustment for all variables which were associated significantly \((P < 0.05)\) with plasma Nt-pro-BNP level in the univariate analysis: age, creatinine clearance, LVEF, plasma peak troponin, gender, anterior wall necrosis, and hypertension.

A multivariable linear regression analysis was performed to analyse the association between plasma Nt-pro-BNP and several variables known to be associated with Nt-pro-BNP. The variables introduced into the model were those that were associated with Nt-pro-BNP with a \(P < 0.20\) in the univariate analysis: creatinine clearance, plasma peak troponin, LVEF, age, gender, diabetes, hypertension, anterior wall necrosis, and STEMI. The multivariable analysis showed that Nt-pro-BNP was negatively associated with creatinine clearance \((P < 0.0001)\) and LVEF \((P < 0.0001)\) and positively associated with plasma peak troponin level \((P < 0.0001)\), age \((P = 0.0016)\), diabetes \((P = 0.0045)\), and female gender \((P = 0.0104)\), but not with hypertension, anterior wall necrosis, or STEMI (Table 2).

When multivariable regression analysis was performed in the subgroup of diabetic patients with MI, Nt-pro-BNP was negatively associated with creatinine clearance \((P = 0.0004)\) and LVEF \((P = 0.0003)\) and positively associated with peak plasma troponin level \((P = 0.0002)\), mean fasting blood glucose \((P = 0.0281)\), and female gender \((P = 0.0375)\) (Table 3).

**In-hospital cardiac events**

During the hospital stay, 43 patients died. In diabetic patients, in-hospital death was significantly higher \((31/199) \text{ vs. } 12/361 \text{ (15.6 vs. 3.3%, } P < 0.0001)\) \((P = 0.009)\) and positively associated with peak plasma troponin level \((P = 0.0002)\), mean fasting blood glucose \((P = 0.0281)\), and female gender \((P = 0.0375)\) (Figure 2).

**Nt-pro-BNP plasma levels and in-hospital outcome**

As shown in Figure 3A, Nt-pro-BNP plasma levels were significantly higher in patients who died at hospital \([800 (147–3915) \text{ vs. } 143 (55–357) \text{ pmol/L, } P < 0.0001]\). Nt-pro-BNP plasma levels were also significantly higher in patients who suffered a cardiogenic shock during in-hospital stay compared with those who did not \([680 (164–1577) \text{ vs. } 137 (53–336) \text{ pmol/L, } P < 0.0001]\) (Figure 3B).
The association between cardiogenic shock and baseline characteristics was studied by multivariable logistic regression analysis. The baseline variables introduced into the model were those that were associated with cardiogenic shock with a $P < 0.20$ in univariate analysis: age, creatinine clearance, systolic blood pressure, diastolic blood pressure, history of MI, diabetes, and Nt-pro-BNP level. When Nt-pro-BNP was not introduced into the model, cardiogenic shock was associated with systolic blood pressure (mmHg) [OR: 0.96 (0.95–0.97); $P < 0.0001$], creatinine clearance < 60 mL/min [OR: 1.54 (1.30–1.82); $P = 0.0125$], and diabetes [OR: 1.45 (1.22–1.72); $P = 0.0364$] but not with age, diastolic blood pressure, and history of MI (Table 4). When Nt-pro-BNP was introduced into the model, cardiogenic shock was associated with Nt-pro-BNP [OR: 2.22

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**Table 1** Patients characteristics

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Diabetic $n = 199$</th>
<th>Non-diabetic $n = 361$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>65 (54.5–75.5)</td>
<td>63.5 (50–75)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Male</td>
<td>137 (69%)</td>
<td>266 (74%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>133 (67%)</td>
<td>171 (47%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28 (25–30)</td>
<td>25 (23–28)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Current smoking</td>
<td>55 (28%)</td>
<td>140 (39%)</td>
<td>0.008</td>
</tr>
<tr>
<td>PVD</td>
<td>23 (12%)</td>
<td>20 (6%)</td>
<td>0.017</td>
</tr>
<tr>
<td>History of MI</td>
<td>42 (21%)</td>
<td>32 (9%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Biological data**

- Fasting glucose (mmol/L) 8.1 (7.1–9.7) 5.3 (5–5.7) <0.0001
- HbA1C (%) 6.9 (6.1–9.4) 5.6 (5.2–5.7) <0.0001
- Creatinine clearance (mL/min) 64 (53–97) 89 (77–113) 0.0002
- Plasma troponin (g/L) 20 (6–41) 20 (5–41) 0.37
- CK-MB (UI/L) 136 (63–341) 114 (47–265) 0.59
- HDL-cholesterol (mmol/L) 1.08 ± 0.36 1.16 ± 0.38 0.0181
- LDL-cholesterol (mmol/L) 2.99 ± 0.92 3.01 ± 1.02 0.90
- Triglycerides (mmol/L) 1.49 (0.87–1.82) 1.27 (0.83–1.62) 0.0157

**Presenting characteristics**

- Heart rate (b/min) 82 (69–97) 75 (65–85) <0.0001
- SBP (mmHg) 140 (120–167) 140 (121–156) 0.37
- DBP (mmHg) 80 (69–92) 80 (68–90) 0.86
- STEMI 132 (66%) 244 (67%) 0.76
- Heart failure 61 (31%) 48 (13%) <0.0001

**Clinical data**

- Anterior wall MI 94 (47%) 151 (42%) 0.22
- LVEF (%) 50 (40–61) 57 (48–65) <0.0001
- LVEF < 40% 49 (25%) 41 (11%) <0.0001

**Treatments**

- CABG 13 (7%) 25 (7%) 0.10
- Primary PCI 44 (38%) 95 (45%) 0.32

Data are expressed as $n$ (%), median (25th and 75th percentile), or mean ± SD.

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**Figure 1** Nt-pro-BNP plasma levels in MI patients with or without diabetes. Data expressed as median (25th–75th).

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**Table 2** Relationship between Nt-proBNP plasma levels and variables assessed by multivariable linear regression in the study population ($n = 560$)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient $\beta$ (SD)</th>
<th>$t$</th>
<th>$P$-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance</td>
<td>-2.30 (0.40)</td>
<td>-5.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(log) (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma peak troponin</td>
<td>0.55 (0.09)</td>
<td>5.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(log) (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (log) (%)</td>
<td>-2.18 (0.46)</td>
<td>-4.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.02 (0.005)</td>
<td>3.17</td>
<td>0.0016</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.35 (0.12)</td>
<td>2.86</td>
<td>0.0045</td>
</tr>
<tr>
<td>(vs. no diabetes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender (vs. male)</td>
<td>0.33 (0.13)</td>
<td>2.57</td>
<td>0.0104</td>
</tr>
</tbody>
</table>

Non-significant variables: hypertension (vs. no hypertension) ($P = 0.54$), anterior wall necrosis (vs. other location) ($P = 0.17$), and STEMI (vs. NSTEMI) ($P = 0.46$).
Plasma peak troponin (log) (μg/L) 0.66 0.17 3.77 0.0002
LVEF (log) (%) −2.69 0.72 −3.69 0.0003
Creatinine clearance (log) (mL/min) −2.26 0.62 −3.64 0.0004
Mean fasting blood glucose (log) (mmol/L) 1.90 0.85 2.22 0.0281
Female gender (vs. male) 0.46 0.222 2.09 0.0375

Table 3: Relationship between NT-proBNP plasma levels and variables assessed by multivariable linear regression in diabetic patients (n = 199)

Variables Coefficient SD t P-values
Mean peak troponin (log) (μg/L) 0.66 0.17 3.77 0.0002
LVEF (log) (%) −2.69 0.72 −3.69 0.0003
Creatinine clearance (log) (mL/min) −2.26 0.62 −3.64 0.0004
Mean fasting blood glucose (log) (mmol/L) 1.90 0.85 2.22 0.0281
Female gender (vs. male) 0.46 0.222 2.09 0.0375

Non-significant variables: age (P = 0.19), anterior wall necrosis (vs. other location) (P = 0.34), STEMI (vs. NSTEMI) (P = 0.77), and hypertension (vs. no hypertension) (P = 0.97).

Discussion

We have shown in the present study from a large non-selected population of patients hospitalized for acute MI that diabetic patients have significantly higher plasma NT-pro-BNP levels and that elevated NT-pro-BNP is strongly associated with the increased incidence of in-hospital mortality and cardiogenic shock.

So far, only a few data are available on plasma NT-pro-BNP levels in diabetic patients. In a general population based study, Raymond et al. found that diabetes was an independent factor associated with increased NT-pro-BNP levels. Moreover, in a very recent cross-sectional study, Magnnuson et al. showed elevated plasma levels of NT-pro-BNP in diabetic patients without overt cardiovascular disease: a 20% increase in NT-pro-BNP median value compared with non-diabetic age-matched subjects. In a cohort of patients with non-ST-elevation acute coronary syndrome, an association between diabetes mellitus and increased plasma NT-pro-BNP levels has also been found. However, no adjustment for LVEF, an important determinant of plasma NT-pro-BNP, was performed in that study. To the best of our knowledge, NT-pro-BNP has never been studied in a population of diabetic patients after acute MI, either in STEMI or in non-STEMI. In the present study, we found a significant increase in plasma NT-pro-BNP in diabetic patients compared with non-diabetic patients. Furthermore, as determined by multivariable regression analysis, diabetes was shown to significantly influence plasma NT-pro-BNP independently of possible confounders such as age, sex, LVEF, creatinine clearance, BMI, hypertension, troponin levels, STEMI, and anterior wall location. Thus, our data indicate that diabetes per se is a strong and independent factor for plasma NT-pro-BNP after MI. Interestingly, we found a 88% increase in NT-pro-BNP median value in diabetic patients after MI when only a 20% increase was observed by Magnnuson et al. in diabetic patients without overt cardiovascular disease, suggesting a strong influence of diabetes on plasma NT-pro-BNP level in acute coronary events.

Our findings are consistent with the previous data showing an increased incidence of cardiogenic shock and in-hospital mortality after MI, in diabetic patients. Moreover, we found a strong association between the plasma NT-pro-BNP level and the level of risk for death or cardiogenic shock after MI. This is a major finding of our study, as it suggests that increased plasma NT-pro-BNP may be one of the links between diabetes and the increased risk for cardiogenic shock after MI. Indeed, in multivariable analysis, diabetes is a significant independent factor for cardiogenic shock when the variable NT-pro-BNP is not introduced into the model but is no more associated with increased risk of cardiogenic shock when NT-pro-BNP is introduced into the model. This result supports the hypothesis that the increased risk of both cardiogenic shock and in-hospital mortality after MI in diabetic patients is linked to elevated NT-pro-BNP levels. Experimental data have showed that BNP and NT-pro-BNP synthetizes are increased not only in the infarcted myocardial tissue but also in surrounding non-infarcted muscle. It has been suggested that the magnitude of the increase in NT-pro-BNP after MI reflects not only the size of the necrosis but also the extent of ischaemic territory.

Indeed, plasma NT-pro-BNP is increased in patients with acute coronary syndrome, even in the absence of necrosis. Moreover, natriuretic peptides transiently increase after exercise-induced ischaemia, proportional to the size of the ischaemic territory. It is suggested that myocardial ischaemia may increase regional wall stretch leading to stimulate NT-pro-BNP secretion. Plasma NT-pro-BNP elevation is also associated with several risk markers associated with adverse outcomes after MI, including advanced age, renal impairment, hypertension, and systolic dysfunction. Thus, plasma NT-pro-BNP elevation seems to reflect the sum or the integral of different risk markers for adverse outcomes following MI with a high informative value.

Several pathophysiological mechanisms might explain the increase in plasma NT-pro-BNP after MI, in diabetic patients. Diabetic patients, even those who are asymptomatic for cardiovascular disease, have frequent and early echographic abnormalities including increased myocardial stiffness, impaired left ventricular compliance, and diastolic dysfunction. ATP deficiency may be responsible for the early
myocardial dysfunction observed in diabetes. Indeed, diabetic patients have an intracellular glucose deficiency leading to impaired production of ATP, which does not allow adequate Na\(^+\)/K\(^+\)-ATPase and Ca\(^{2+}\)-ATPase functions. This modification of ion pumps leads to impaired relaxation in the myocardium,\(^3\) which could account for the increased Nt-pro-BNP secretion. Such metabolic features for increased Nt-pro-BNP in diabetes could also explain the independent association between fasting glycaemia and Nt-pro-BNP levels found in our study. Moreover, hearts from diabetic patients are known to have an increased collagen content which may increase Nt-pro-BNP secretion from diabetic myocardium.\(^3\) It has also been suggested that the increase in Nt-pro-BNP after MI partially reflects the extent of ischaemic territory;\(^4\,6\) therefore, the elevated plasma Nt-pro-BNP levels observed in diabetic patients could be the consequence of the greater extent of the severity of ischaemia when compared with non-diabetic patients, even with a similar infarct size. Autopsic data have shown a lower capillary density in the myocardium of diabetic patients who died from MI, which could partly explain the severity of ischaemia.\(^3\) Furthermore, endothelium dysfunction, which has been reported in diabetic patients, could also be involved in the extent of ischaemia.\(^3\) Indeed, the incidence of death and heart failure has been shown to be significantly increased in diabetic patients despite similar or smaller infarct size.\(^3\,4\,6\)

**Study limitation**

As the diabetes definition of the present study was partly based on elevated fasting glycaemia, our results could not
be applicable to solely established diabetes, as hyperglycaemia during MI is not pathognomonic of the diabetic disease. In order to investigate the robustness of the analysis among patients with solely established diabetes, we compared the baseline characteristics of the diabetic group (defined by established and elevated glycaemia) \( (n = 199) \) vs. patients with solely established diabetes \( (n = 129) \) and found no significant difference between the two groups for baseline characteristics, i.e. median age (65 years in the two groups, \( P = 0.76 \)), sex ratio (male: 71 vs. 69, \( P = 0.84 \)), median NT-pro-BNP levels (202 vs. 245 pmol/L, \( P = 0.19 \)), and for in-hospital death (12 vs. 16\%, \( P = 0.40 \)) and cardiogenic shock (13 vs. 18\%, \( P = 0.18 \)). Thus, these findings suggest that our analysis is robust not only for the diabetic population, as defined according to the presence of either established diabetes or hyperglycaemia, as ADA defined, but also for the solely established diabetes.

## Conclusions

We have shown in the present study from a large population of patients hospitalized for acute MI that diabetes \textit{per se} is a strong and independent factor for plasma NT-pro-BNP levels. Furthermore, elevated NT-pro-BNP is strongly associated with the increased incidence of in-hospital mortality and cardiogenic shock observed in diabetes, after MI, indicating that plasma NT-pro-BNP provides highly valuable prognostic information on in-hospital outcome in this population.

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### References


