Diabetes mellitus type 2 and angina pectoris: novel insights in diagnosis, prognosis and treatment

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NT-pro-BNP is independently associated with myocardial ischemia in mildly symptomatic type 2 diabetic patients

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Mieke D Trip
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Submitted
Abstract

Purpose
Baseline levels of N-terminal fragment of the brain natriuretic peptide prohormone (NT-pro-BNP) are associated with myocardial ischemia in non-diabetic patients with stable angina pectoris. The aim of this study was to assess the relation between NT-pro-BNP and myocardial ischemia in type 2 diabetic patients with angina pectoris.

Methods
A total of 281 patients with diabetes mellitus type 2 and stable angina pectoris underwent myocardial perfusion scintigraphy (MPS). NT-pro-BNP was determined before MPS.

Results
Myocardial ischemia on MPS was present in 140 (50%) patients. These ischemic patients had significantly higher NT-pro-BNP levels compared with patients without ischemia: 182.8pg/ml (63.8-323.6) vs. 88.4pg/ml (34.3-207.1), respectively (p<0.001). NT-pro-BNP ≥180pg/ml was an independent predictor of the presence of myocardial ischemia (OR 2.36, 95%CI 1.40-3.97, p=0.001).

Conclusions
Increased levels of NT-pro-BNP are independent, albeit moderate, predictors of myocardial ischemia in these type 2 diabetics with mild anginal complaints. The clinical value of NT-pro-BNP for stratification purposes is of limited value in this patient population.
Introduction

To date, approximately 150 million people worldwide are diagnosed with type 2 diabetes mellitus and this number is expected to double before 2025. Diabetic patients are at a 2-4 fold higher risk of developing coronary artery disease (CAD) and approximately 75% of diabetics will die from a cardiac cause. Moreover, diabetic patients are more likely to have an atypical or less distinct expression of their anginal symptoms, and myocardial ischemia is already present in ±20% of asymptomatic patients. To install proper dietary and lifestyle adaptation, pharmacological risk factor modification and optimization of anti-anginal treatment, attempts must be made to identify diabetic patients with CAD at an early stage, possibly even before anginal complaints becomes overt.

Brain-type natriuretic peptide (BNP) and the N-terminal fragment of its pro-hormone (NT-pro-BNP) are neurohormones with diuretic, vasodilatory and renin-angiotensin-aldosterone antagonist effects, secreted primarily by cells in the ventricular wall in response to increased wall stress. These markers are known to predict disease state and prognosis in patients with heart failure and are of value in the diagnosis and prognosis of patients with acute coronary syndromes. Recent studies stated that increased NT-pro-BNP levels are associated with myocardial ischemia in non-diabetic patients with stable anginal complaints. Furthermore, increased levels of BNP were related to exercise induced ischemia in asymptomatic diabetic patients. The extrapolation of this association to patients with diabetes mellitus type 2 and mild stable anginal complaints seems likely but has not been studied yet. Therefore the aim of our study was to assess the association between NT-pro-BNP and myocardial ischemia in type 2 diabetic patients with stable mild anginal complaints (Canadian Cardiovascular Society (CCS) class I-II/IV). Furthermore we tried to determine the additional value of NT-pro-BNP in identifying those patients with myocardial ischemia.

Methods

Setting
The study population consisted of patients who had been screened for inclusion in the randomized multicenter MERIDIAN (Multicenter trial of Elective Revascularization in patients with Diabetes mellitus and mild Anginal symptoms) trial. Detailed descriptions
of the study design and of the principal results have been published previously\textsuperscript{18}. In this randomized trial, patients with diabetes mellitus type 2, mild anginal complaints (CCS class I-II/IV) and without an indication for coronary revascularization were eligible for screening. The patients were recruited from the Cardiology and Internal Medicine outpatient clinics in 20 Dutch hospitals (see appendix A for the list of participating centers). All patients underwent a myocardial perfusion scintigraphy (MPS) to detect the presence of myocardial ischemia. Only patients with myocardial ischemia on MPS were eligible for randomization to an early invasive approach including coronary angiography and revascularization if feasible or an optimized continued medical treatment. All patients underwent initial clinical and laboratory evaluation prior to MPS. The trial complied with the Declaration of Helsinki. The medical ethical committees of the participating centers approved the protocol and all patients gave written informed consent before MPS.

In this sub analysis, the level of NT-pro-BNP was related to the presence of myocardial perfusion defects on MPS.

**Patient population**

Inclusion and exclusion criteria have previously been described\textsuperscript{18}. In short patients \(\geq30\) years with mild, stable (\(\geq2\)months) complaints of angina pectoris (CCS class I-II/IV) and type 2 diabetes mellitus were eligible for screening. Type 2 diabetes mellitus was defined as the presence of one or more of the following: fasting glucose of \(>7.0\) or non-fasting of \(>11.0\) mmol/L in 2 samples on 2 separate days, treatment with oral antidiabetic medication, treatment with oral medication combined with insulin, or onset of insulin treatment at age \(\geq50\) years. Patients were excluded if they had heart failure or an ejection fraction <35\% (as measured by echocardiography or gated MPS) or had a plasma creatinine level \(>250\mu\text{mol/L}\).

**Myocardial perfusion scintigraphy and image analysis**

Stress and rest myocardial perfusion scintigraphy (with single-photon emission computed tomography (SPECT)) was performed with \(^{99m}\text{Tc}\) labeled perfusion tracers (Tetrofosmin or sesta-MIBI) or Thallium-201, according to the guidelines of the American Society of Nuclear Cardiology \textsuperscript{19}. The use of ECG-gated SPECT was not mandatory and was at the discretion of the nuclear physician.

Symptom limited exercise (bicycle or treadmill ergometry) was the preferred stress modality. Pharmacological vasodilatory stress with adenosine or dipyridamole was applied if there was insufficient increase of heart rate (\(<85\%\) age predicted maximal
heart-rate) during physical exercise, in the presence of a left bundle branch block, or if the anti-anginal medication had not been adequately discontinued. Dobutamine stress testing was performed in patients with a contra-indication for adenosine or dipyridamole.

A local panel of 2-3 nuclear physicians analyzed the images using a 17 myocardial segment model. Segments were scored with a 5-point scoring system (0=normal; 1=equivocal; 2=moderate reduction; 3=severe reduction; 4= absent activity). Summed stress score (SSS) and summed rest score (SRS) were obtained by adding the scores of all segments of respectively stress and rest images. The summed difference score (SDS) was calculated by subtracting the SRS from the SSS. Reversible myocardial perfusion defects were defined as SDS ≥3. These reversible defects are indicative for inducible myocardial ischemia, and will be referred to as myocardial ischemia.

Biochemical analysis
Fasting serum samples were collected in heparin-coated tubes before the MPS, centrifuged without delay (≤1 hour) and stored at −80°C until further analysis. A Roche Diagnostics (Mannheim, Germany) Modular P-800 instrument was used for photometrical measurement of serum creatinine (Crea plus, Roche Diagnostics, Mannheim, Germany) and Modular E-170 system was used for the chemiluminescent measurement of NT-pro-BNP (Roche Diagnostics, Mannheim, Germany). The lower detection limit of the NT-pro-BNP assay is 5pg/ml and all values <5pg/ml were designated as 2.5pg/ml for statistical analysis. Creatinine clearance was calculated using the Cockroft-Gault formula. An abnormal creatinine clearance was defined as a glomerular filtration rate (GFR) of <75ml/min/1.73m².

Statistical analysis
Data are presented as number of patients (%), mean (standard deviation) or as median (interquartile range). Continuous variables were compared by Student’s unpaired t test, Mann-Whitney test or one-way ANOVA; categorical variables were compared by χ² or Fisher’s exact test where appropriate. NT-pro-BNP levels had a skewed distribution and were therefore log transformed. Tables show untransformed medians and corresponding interquartile range (IQR). Receiver-Operator-Curves (ROC) analysis was used to evaluate the performance of NT-pro-BNP to identify patients with myocardial ischemia. The best cut-off value was defined as the highest sum of sensitivity and specificity. Binary logistic regression analysis was performed to assess the additional
value of NT-pro-BNP in the prediction of myocardial ischemia on MPS, in addition to known clinical predictors. The SPSS package for windows version 12.0 (SPSS Inc, Chicago, IL, USA) was used for these purposes. Values of p<0.05 were considered statistically significant.

**Results**

**Patient population**
Between October 2002 and July 2004, 329 patients from 20 Dutch hospitals underwent ischemia detection by MPS for the MERIDIAN trial. The current analysis was based on the 281 patients of whom blood samples were available.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>All patients, n=281</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>183 (65)</td>
</tr>
<tr>
<td>Age</td>
<td>64.6 (9)</td>
</tr>
<tr>
<td>CCS II/IV</td>
<td>114 (41)</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>6.6 (0.02-38.1)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.3 (4)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>49 (17)</td>
</tr>
<tr>
<td>Previous smoking</td>
<td>146 (52)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>154 (55)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>178 (63)</td>
</tr>
<tr>
<td>Family history</td>
<td>102 (36)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>136 (48)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>85 (30)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>78 (28)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>51 (18)</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>236 (84)</td>
</tr>
<tr>
<td>Statin</td>
<td>207 (74)</td>
</tr>
<tr>
<td>ACE-inhibition</td>
<td>113 (40)</td>
</tr>
<tr>
<td>Beta-blockade</td>
<td>205 (73)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>119 (42)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>111 (40)</td>
</tr>
<tr>
<td>Insulin</td>
<td>110 (39)</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics. Values are presented as number (%) or as median (min-max). CCS=Canadian Cardiovascular Society; CAD=coronary artery disease; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting.
Baseline characteristics of these patients are described in Table 1. The population consisted predominantly of male patients (mean age 65 ±9 years). The mean body mass index was 29.4 kg/m². The duration of diabetes mellitus was 6.6 years (IQR 3.3-11.6) and 39% of patients needed insulin to regulate their blood glucose. Approximately half of the population already had a known cardiovascular medical history, and the majority was taking aspirin, lipid-lowering therapy and beta-blockers.

Myocardial perfusion scintigraphy
All 281 patients underwent myocardial perfusion scintigraphy. Symptom limited exercise was performed in 175 (62%) patients, pharmacological stress (adenosine or dipyridamole) was used in 99 (35%) patients. Of the 281 patients, 197 (70%) patients had an abnormal MPS: 140 patients had myocardial ischemia, of whom 75 (27%) also had evidence of fixed defects (scar-tissue), and 57 (20%) patients had only fixed defects. Gated SPECT results were available in 130 patients (79 patients without and 51 patients with myocardial ischemia). The mean post-stress left ventricular ejection fraction was 60%±12. In patients with myocardial ischemia, left ventricular ejection fraction (LVEF) was significantly lower compared with patients without ischemia, 57%±10 vs. 62%±12, respectively (p=0.04).

Biochemical analysis
The overall median levels were: NT-pro-BNP 118pg/ml (IQR 46-278), high-sensitive C-reactive protein (hs-CRP) 2.2mg/L (IQR 1.1-4.3) and GFR 79ml/min/1.73m² (IQR 65-98). NT-pro-BNP levels were significantly higher in the 140 patients with myocardial ischemia (Table 2).
ischemia, compared with the 141 patients without (183 pg/ml (IQR 64-324) vs. 88 pg/ml (IQR 34-207), p=0.001, Table 2). There was an increase in NT-pro-BNP levels from patients without any perfusion abnormalities, patients with only fixed defects to patients with myocardial ischemia (Table 2). NT-pro-BNP levels in patients without any perfusion abnormalities were significantly lower compared to those patients with only fixed defects and those with myocardial ischemia. No difference was found in NT-pro-BNP levels between patients with only fixed defects and patients with myocardial ischemia. No differences were observed in levels of high sensitive-CRP, or creatinine clearance (expressed as GFR) between patients with or without myocardial ischemia.

**Figure 1.** Receiver-operator-curve (ROC) for NT-pro-BNP as a predictor of myocardial ischemia.

![ROC curve](image)

**Association between MPS results and NT-pro-BNP levels**

Figure 1 shows the ROC-curve for NT-pro-BNP as a predictor of myocardial ischemia. The area under the curve (AUC) was 0.62 (95% CI 0.55-0.68), p<0.001. The best cut-off value for NT-pro-BNP was determined at 180 pg/ml. This cut-off value yielded a sensitivity of 52%, specificity of 72%, negative predictive value of 60%, positive predictive value of 65% and an accuracy of 62%.

Patients with levels of NT-pro-BNP ≥ 180 pg/ml were older (61.9 ± 8.5 vs. 68.9 ± 8.2 yrs, p<0.001), more likely to have a history of CAD (MI or revascularization) (70 (41%) vs. 66 (60%), p=0.003) and more often had a GFR rate below 75 ml/min/1.73 m² (55 (33%) vs. 69 (64%), p<0.001).

The unadjusted OR of NT-pro-BNP ≥180 pg/ml for the prediction of myocardial ischemia was 2.60, 95%CI 1.59-4.26; p<0.001 (χ²=14.8, p<0.001). After adjusting for known clinical predictors of myocardial ischemia in this population (male gender,
the use of 2 or more different anti-anginal drugs, a history of MI without a history of revascularization, and the absence of statin therapy\textsuperscript{20}, NT-pro-BNP \( \geq 180 \text{pg/ml} \) remained an independent predictor of inducible myocardial ischemia on top of these variables (OR 2.49, 95\%CI 1.49-4.17, \( p=0.001 \)) (model 1, table 3). Furthermore, the

Table 3. Multivariate models of the value of NT-pro-BNP for the prediction of myocardial ischemia

<table>
<thead>
<tr>
<th>Model</th>
<th>( \chi^2 )</th>
<th>OR</th>
<th>95%CI</th>
<th>\textit{p}-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Model</td>
<td>31.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>3.02</td>
<td>(1.77-5.15)</td>
<td>\textless 0.001</td>
<td></td>
</tr>
<tr>
<td>( \geq 2 ) different anti-anginal drugs</td>
<td>2.32</td>
<td>(1.40-3.83)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Statin therapy</td>
<td>0.52</td>
<td>(0.29-0.92)</td>
<td>\textless 0.03</td>
<td></td>
</tr>
<tr>
<td>MI, no revascularization</td>
<td>2.33</td>
<td>(0.89-6.05)</td>
<td>\textless 0.08</td>
<td></td>
</tr>
</tbody>
</table>

Additional value of NT-pro-BNP \( \geq 180 \text{pg/ml} \)

Model 1. 41.72

| NT-pro-BNP | 2.49 | (1.49-4.17) | 0.001        |
| Male gender | 2.82 | (1.65-4.81) | \textless 0.001 |
| \( \geq 2 \) different anti-anginal drugs | 1.95 | (1.18-3.22) | 0.01          |
| Statin therapy | 0.55 | (0.30-1.00) | 0.051        |
| MI, no revascularization | 2.23 | (0.83-5.98) | 0.11          |

Model 2. 41.66

| NT-pro-BNP | 2.60 | (1.54-4.40) | \textless 0.001 |
| Male gender | 2.80 | (1.63-4.82) | \textless 0.001 |
| \( \geq 2 \) different anti-anginal drugs | 1.93 | (1.16-3.21) | 0.01 |
| Statin therapy | 0.54 | (0.29-1.00) | 0.051 |
| MI, no revascularization | 2.47 | (0.88-6.99) | 0.09 |
| GFR < 75 ml/min/1.73 m\(^2\) | 0.95 | (0.55-1.64) | 0.85 |
| hs-CRP \( \geq 3 \) mg/L | 0.87 | (0.50-1.51) | 0.62 |

Model 3. 48.91

| NT-pro-BNP | 2.58 | (1.52-4.36) | \textless 0.001 |
| Male gender | 2.83 | (1.64-4.86) | \textless 0.001 |
| \( \geq 2 \) different anti-anginal drugs | 1.90 | (1.14-3.17) | 0.01 |
| Statin therapy | 0.51 | (0.25-1.04) | 0.09 |
| MI, no revascularization | 3.01 | (1.02-8.80) | 0.05 |
| GFR < 75 ml/min/1.73 m\(^2\) | 0.94 | (0.49-1.83) | 0.86 |
| hs-CRP \( \geq 3 \) mg/L | 0.86 | (0.49-1.52) | 0.60 |

Table 3. Multivariate logistic regression model. \( \chi^2 = \) predictive value of the model; OR= odds ratio; CI= confidence interval; GFR= glomerular filtration rate; hs-CRP= high sensitive C-reactive protein. Model 3 after adjustment for the following possible cardiac risk factors: age>65yrs; use of insulin; hypertension; hypercholesterolemia; smoking; family history of CAD; BMI>29.7; duration of diabetes > 5 yrs.
predictive value of this model was higher compared with the clinical model alone ($\chi^2$ 31.61 vs. $\chi^2$ 41.72, p<0.001). Neither a GFR <75ml/min/1.73m$^2$, nor hs-CRP ≥3mg/L contributed further to the prediction of inducible myocardial ischemia on MPS (model 2, Table 3). No interaction-term between GFR or hs-CRP and NT-pro-BNP was observed. Adjustment for possible cardiac risk factors further improved the predictive value of the model (model 3, Table 3).

In the 130 patients with available gated SPECT results, the predictive value of NT-pro-BNP remained significant after further adjustment for LVEF (OR 4.23, 95%CI 1.86-9.66, p=0.001). LVEF was not a predictor for myocardial ischemia (OR 0.93, 95%CI 0.17-5.00, p=ns), and no interaction-term was observed between the LVEF and NT-pro-BNP.

**Discussion**

In this study, we demonstrated that NT-pro-BNP levels ≥180pg/ml provide independent diagnostic information regarding the presence of myocardial ischemia in diabetic patients with stable angina pectoris.

**NT-pro-BNP and myocardial ischemia**

The current belief is that NT-pro-BNP is released in relation to increased ventricular wall stress. Because left ventricular filling pressure also increases during (inducible) myocardial ischemia, this may lead to a release of BNP and NT-pro-BNP. Several studies have reported on the relation between elevated baseline NT-pro-BNP levels and myocardial ischemia in different patient populations, presenting with non-acute anginal complaints. Furthermore, Rana et al described a positive relation between silent ischemia as assessed with exercise testing and BNP in asymptomatic diabetic patients. However, to our knowledge, this is the first study to demonstrate a positive association between baseline NT-pro-BNP and myocardial ischemia in patients with only mild anginal complaints. Diabetic patients are known to have more extensive and diffuse atherosclerotic disease with micro-vascular involvement, left main disease and multi-vessel disease, even when anginal complaints are absent, possibly resulting in higher levels of NT-pro-BNP even without complaints. Moreover, patients with diabetes more often have asymptomatic ischemic episodes. Furthermore, NT-pro-BNP levels are related to the extent of the ischemic territory. The ischemic burden and the subsequent NT-pro-BNP rise, in diabetic patients may therefore be higher compared to non-diabetics.
Several reports have shown that plasma NT-pro-BNP levels are elevated in association with diabetes mellitus \textsuperscript{28-30}. These changes in brain natriuretic peptides are thought to be associated with the progression of cardiovascular disease rather than with the diabetic disease itself \textsuperscript{30, 31}. However, in most studies on diabetic patients the median NT-pro-BNP levels fluctuated around 30-50pg/ml, this not in line with our findings \textsuperscript{28, 29, 32}. In a relative recent study by Beer et al, NT-pro-BNP levels were reported more comparable with our results (120pg/ml) \textsuperscript{33}. The higher levels NT-pro-BNP in both the study of Beer et al. and our own study might be explained by the fact that in both studies patients with micro- and macrovascular complications, as well as patients with micro-albuminuria and mild hypertension were included. Furthermore, our patients were older and more often male, factors known to increase the levels of NT-pro-BNP \textsuperscript{30, 31, 34, 35}. Our study population excluded patients with a decreased left ventricular ejection fraction, and or unstable angina, which are other factors associated with higher levels of NT-pro-BNP.

**Confounding variables and NT-pro-BNP**

NT-pro-BNP was an independent predictor of myocardial ischemia on MPS and possible confounding factors such as age, GFR and LVEF were of no influence on the predictive value in this specific patient population. This can be explained by the fact that the patient population consisted of a highly selected group of patients, without a history of renal failure and creatinine levels of <250μg/L. Furthermore, patients with LVEF<35\% or with dyspnea (NYHA III-IV/IV) were also excluded from this randomized trial.

**NT-pro-BNP and the prediction of myocardial ischemia**

Although NT-pro-BNP is an independent predictor of myocardial ischemia as assessed with MPS, the sensitivity and specificity and especially the negative predictive value for the detection of myocardial ischemia were rather low. NT-pro-BNP has a limited predictive value for presence or absence of myocardial ischemia. Furthermore, the cut-off value of 180pg/ml is the optimal choice given the current dataset. We cannot exclude the possibility that the sensitivity and specificity would be even lower if we would replicate our study in a different patient population. However, the test characteristics of NT-pro-BNP in relation to the presence of myocardial ischemia as found in our study are in accordance with previous studies \textsuperscript{12, 24}. Although these studies used coronary angiography as a reference, the similar findings strengthen the idea that NT-pro-BNP as a stand-alone test for CAD is of limited value in patients with stable angina pectoris.
Conclusion and clinical implications
Increased levels of NT-pro-BNP are independent, albeit moderate, predictors of myocardial ischemia in patients with type 2 diabetes mellitus and mild, stable anginal complaints. The clinical utility of NT-pro-BNP for diagnostic purposes in this patient population is of limited value.

Grant/funding support
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Acknowledgments
We thank all investigators and coordinators of the MERIDIAN trial, all nuclear physicians, all clinical chemists and laboratory staff, and the medical and nursing staff in the recruitment and intervention centers who made the trial possible.
APPENDIX A.

The following investigators and research coordinators, all in the Netherlands, enrolled patients in the MERIDIAN trial:
Amsterdam, Academic Medical Center - J. J. Piek;
Amsterdam, OLVG - G. J. Laarman;
Amsterdam VU Medical Center - G. Veen, J.G.F Bronzwaer;
Amsterdam, Slotervaart Hospital - C.A. de Groot, C.E. Schotborgh;
Amsterdam, St. Lucas-Andreas Hospital - A.R.Willems;
Amsterdam, Boven-IJ Hospital - A.L.M. Bakx;
Amstelveen, Amstelland Hospital - W.L. ten Holt;
Almere, Flevo Hospital - A.S.J.M. Sadee;
Apeldoorn, Gelre Hospitals - W.T.J. Jap Tjoen San;
Blaricum, Gooi-Noord Hospital - G. Hoedemaker;
Breda, Amphia Hospital - P.H.J.M. Dunselman;
Eindhoven, Catharina Hospital - R.H. Michels;
Groningen, Academic Medical Center - F.Zijlstra;
Haarlem, Kennemer Hospital, location EG - B. de Vlies, G. Kan;
Hengelo, Midden Twente Hospital - A. Derks;
Hoorn, Westfries Gasthuis Hospital - C.L. Janus, D.C.G. Basart;
Maastricht, Academic Medical Center - C. de Zwaan, F.W.H.M Bär;
The Hague, Medical Center Haaglanden - L.H. Savalle;
Reference List


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(34) Raymond I, Groenning BA, Hildebrandt PR et al. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. *Heart* 2003 July;89(7):745-51.