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Serum NT-proBNP and Risk of Cognitive Decline

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Chapter 7 – Serum NT-proBNP and Risk of Cognitive Decline

Summary

N-terminal pro-brain natriuretic peptide (NT-proBNP) has been related with cognitive impairment, which might be explained by clinical heart failure. Whether NT-proBNP associates with cognitive decline independent of clinical heart failure has not been studied. We investigated the association of NT-proBNP with cognitive decline in older subjects without advanced stages of clinical heart failure. We studied 5205 men and women (mean age 75 years) at high cardiovascular risk without prevalence or incidence of advanced stages of clinical heart failure (defined as New York Heart Association functional class III/IV at baseline or heart failure hospitalization during follow-up) of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Four domains of cognitive function were tested at baseline and repeated during a follow-up period of 3.2 years. Participants with higher NT-proBNP levels ($\geq$ 450 ng/L) had a worse baseline cognitive function on all tests, including reaction time (mean difference high vs. low group (95% CI)) 2.84 seconds (0.60; 5.08); processing speed -0.94 digits coded (-1.57; -0.31); immediate memory -0.11 pictures remembered (-0.28; 0.06); and delayed memory -0.13 pictures remembered (-0.36; 0.11). Longitudinally, participants with higher NT-proBNP levels had a steeper cognitive decline during follow-up, including reaction time (mean annual change high vs. low group (95% CI)) 0.61 seconds (0.15; 1.07); processing speed -0.15 digits coded (-0.25; -0.05); immediate memory -0.05 pictures remembered (-0.09; 0.00); delayed memory -0.05 pictures remembered (-0.11; 0.01). Higher NT-proBNP levels associate with a steeper cognitive decline in older subjects without advanced stages of clinical heart failure. Although the exact underlying mechanism is unclear, NT-proBNP may serve as a biomarker of suboptimal left ventricular function, resulting in cognitive decline.
Higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a hormone produced by cardiomyocytes in response to ventricular stretch, have been associated with cognitive impairment. Evidence comes from several cross-sectional studies, which show that among community-dwelling older subjects, higher NT-proBNP levels were associated with worse cognitive function, in particular memory. There are a limited number of longitudinal studies with relatively small sample sizes, which demonstrate that higher NT-BNP levels are also associated with steeper declines in Mini-Mental State Examination (MMSE) scores and higher incidence of dementia. A potential mechanism behind the relationship between higher NT-proBNP levels and cognitive function is clinical heart failure, resulting in left ventricular dysfunction with subsequent reduced cardiac output. It is hypothesized that reduced cardiac output causes inadequate cerebral perfusion, leading to a higher risk of cognitive impairment.

Improvements in cognitive function in patients following cardiac transplantation suggests that impaired cardiac function might be a reversible risk factor for cognitive impairment.

Recent evidence demonstrates that higher NT-proBNP levels in older subjects without clinical heart failure are strongly associated with cardiovascular diseases and risk factors and predict an increased risk of atrial fibrillation, stroke, transient ischemic attack, myocardial infarction and mortality. In addition, higher NT-proBNP levels have been related to left ventricular hypertrophy and systolic and diastolic dysfunction in subjects without clinical heart failure. The relationship of cardiovascular diseases and risk factors with cognitive impairment is well-established. Hence, cognitive impairment might already be present in asymptomatic subjects at early stages of reduced cardiac function. However, the association of higher NT-proBNP levels with cognitive impairment and decline in subjects without advanced stages of clinical heart failure has not been studied yet.

We hypothesized that elevated levels of NT-proBNP are associated with a steeper cognitive decline, even in subjects without the prevalence or incidence of advanced stages of clinical heart failure. Therefore, we studied the association of NT-proBNP with cognitive function cross-sectionally and longitudinally in a cohort of older men and women from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), in which participants with advanced heart failure, defined as New York Heart Association (NYHA) functional class III/IV at baseline or heart failure hospitalization during follow-up, were not included.
Methods

Study design

Data in this study were obtained from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older men and women with pre-existing cardiovascular disease or risk factors thereof. This trial included 5,804 individuals aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. Approximately 50% of the participants showed evidence of cardiovascular disease including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and vascular surgery. The rest of participants had one or more cardiovascular risk factor, defined as hypertension, smoking or diabetes mellitus. Primary outcome of the trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years. The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent\textsuperscript{19,20}.

Study participants

Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were excluded from PROSPER\textsuperscript{19}. For the present study, we additionally excluded participants with heart failure hospitalization during follow-up (n=205).

Serum NT-proBNP

Blood samples were taken at 6 months after follow-up in EDTA tubes. NT-proBNP was determined using electrochemiluminescence immunoassay on a Roche Modulator E170. A number of 394 participants had missing NT-proBNP measurements. In keeping with existing literature on cutoff values in this age group, we defined three groups of NT-proBNP: low (<100 ng/L), middle (100-450 ng/L) and high NT-proBNP ($\geq$ 450 ng/L)$^1$.

Cognitive function
The MMSE was used to evaluate global cognitive function; participants with a baseline score below 24 points were excluded from PROSPER. Cognitive function was tested at baseline and at 9, 18, 30 months and at the end of the study. The time-point of the measurement at the end of the study varied between 36 and 48 months; therefore, we performed the analysis with their individually varying time point, but report the results for the mean of these time points (at 42 months). Four different neuropsychological tests were used to assess executive function, attention, immediate and delayed memory. The Stroop-Colour-Word-Test was used to test selective attention and reaction time of the participants. The participants were asked to read a color name which was displayed in a color different from the color it actually names. The outcome parameter was total number of seconds to complete the test; a higher score therefore indicates worse performance. General cognitive speed was tested by the Letter-Digit Coding Test. The participants had to match certain digits with letters according to a provided key. The outcome variable was the total number of correct entries in 60 seconds, and therefore higher scores represented better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory performance. Fifteen pictures were presented at the participants, and they were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the test to measure their delayed recall. The outcome parameter is the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests and the procedures has been published previously\textsuperscript{21}. Since treatment with pravastatin did not influence cognitive function during follow-up, we included participants from both pravastatin and placebo groups\textsuperscript{22}.

Statistical analysis

Baseline characteristics of the study participants are reported as mean (standard deviation) for continuous variables and number (percentage) for categorical variables for each group of NT-proBNP. Differences in continuous variables were tested with linear regression models, in which p-values were calculated using log-transformed NT-proBNP levels. Differences in categorical variables were tested by Chi-squared tests.

To investigate the cross-sectional association of NT-proBNP with cognitive function, we used linear regression models. Log transformed NT-proBNP levels were included as independent variable; outcome variable was the mean baseline score on each of the four cognitive function tests. Linear mixed models were used to examine the association between NT-proBNP and cognitive decline over
time. The models included log transformed NT-proBNP levels, time (in years) and the interaction term between time and log transformed NT-proBNP levels. We performed our analyses in three steps. In the first step, crude analyses were performed, in which we only adjusted for cognitive test version where appropriate. In the second step, we added the variables age, sex, education, country and apolipoprotein E genotype to the model to investigate the potential influence of these factors on the associations (minimally adjusted model). Furthermore, in a fully adjusted model we also added the following potential confounders: cardiovascular diseases and risk factors at baseline (history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, smoking status, HDL and LDL cholesterol levels, triglycerides, systolic and diastolic blood pressure, body mass index), statin treatment and serum creatinine level. Since the associations did not essentially change in different models, results of the minimally and fully adjusted models are presented in the manuscript. To further explore the influence of cardiovascular diseases and risk factors, additional analyses were performed in which we stratified for history of cardiovascular diseases and risk factors. To test whether the difference between participants with or without a history of cardiovascular disease or risk factor was significant, we calculated a p-value for interaction by using linear regression models. Furthermore, we performed additional sensitivity analyses in which we excluded 1) participants taking pravastatin treatment during follow-up; 2) participants with incident stroke and/or transient ischemic attack during follow-up; 3) participants with incident myocardial infarction during follow-up; 4) participants with incident atrial fibrillation during follow-up; 5) participants with vascular events, including coronary heart disease death, nonfatal myocardial infarction, nonfatal and fatal stroke and/or TIA during follow-up; and 6) participants taking loop diuretics, beta blockers or ACE-inhibitors at baseline.

Results

Table 1 shows baseline characteristics of study participants grouped by NT-proBNP levels. Participants with higher NT-proBNP levels were older and had a higher prevalence of hypertension, myocardial infarction, vascular disease and smoking (all p-values <0.001). Body mass index was lower in participants with higher NT-proBNP levels (p-value <0.001). Systolic blood pressure, pulse pressure and mean arterial blood pressure were higher among participants with higher NT-proBNP levels (p-values <0.001, p<0.001 and p=0.001 respectively). Furthermore, use of loop diuretics, beta blockers and ace-inhibitors was higher in participants with higher NT-proBNP levels (p-values <0.001, p<0.001 and
p=0.031 respectively). Participants with higher NT-proBNP levels had higher creatinine levels (p < 0.001).

Table 2 shows the association of NT-proBNP levels with cognitive function at baseline. In the minimally adjusted model, participants with higher NT-proBNP levels had a worse performance on Stroop test (p=0.004) and Letter-Digit Coding test (p<0.001). The same trend was observed for immediate and delayed Picture-Word Learning tests, showing that participants with higher NT-proBNP levels had worse performance, albeit these associations were not significant (p-value=0.062 and p=0.065 respectively). When further adjusting for prevalent cardiovascular diseases or risk factors at baseline, we found similar differences in cognitive function between the groups. The association of NT-proBNP levels with Stroop test and Letter-Digit Coding test in the fully adjusted model remained significant (p-value=0.005 and p<0.001 respectively), whereas for immediate and delayed Picture-Word Learning tests the associations did not significantly differ (p-value=0.115 and p=0.083 respectively). Results from adjusted models did not materially differ from crude models.
### Table 1. Baseline characteristics of study participants grouped by NT-proBNP

<table>
<thead>
<tr>
<th>NT-proBNP (ng/L)</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1818</td>
<td>N=2698</td>
<td>N=689</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 ng/L</td>
<td>100-450</td>
<td>≥450 ng/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Demographics
- Age, years: 74.42 (3.04) | 75.53 (3.37) | 76.59 (3.40) | <0.001
- Female, n (%): 850 (46.8) | 1490 (55.2) | 360 (52.2) | <0.001
- Age left school, years: 15.17 (2.06) | 15.15 (2.06) | 15.10 (2.08) | 0.083

#### Vascular risk factors
- Hypertension, n (%): 1056 (58.1) | 1736 (64.3) | 444 (64.4) | <0.001
- Diabetes mellitus, n (%): 245 (13.5) | 245 (9.1) | 57 (8.3) | <0.001
- Stroke or TIA, n (%): 189 (10.4) | 301 (11.2) | 85 (12.3) | 0.371
- Myocardial infarction, n (%): 630 (34.7) | 1246 (46.2) | 393 (57.0) | <0.001
- Current smoker, n (%): 536 (29.5) | 667 (24.7) | 175 (25.4) | 0.001
- Body mass index, kg/m²: 27.22 (4.02) | 26.69 (4.21) | 26.17 (4.20) | <0.001
- Total cholesterol, mmol/L: 5.68 (0.90) | 5.68 (0.91) | 5.70 (0.93) | 0.461
- Systolic blood pressure, mmHg: 152.60 (20.25) | 155.11 (21.75) | 158.75 (23.50) | <0.001
- Diastolic blood pressure, mmHg: 84.02 (10.95) | 83.73 (11.33) | 83.38 (12.01) | 0.158
- Pulse pressure, mmHg: 68.58 (0.42) | 71.38 (0.35) | 75.37 (0.68) | <0.001
- Mean Arterial Pressure, mmHg: 106.88 (0.30) | 107.53 (0.25) | 108.51 (0.49) | 0.001

#### Antihypertensive medications, n (%)
- Diuretics: 650 (35.8) | 1067 (39.5) | 269 (39.0) | <0.001
- Loop: 153 (8.4) | 327 (12.1) | 107 (15.5) | < 0.001
- Other: 497 (27.3) | 740 (27.4) | 162 (23.5) | 0.125
- Calcium channel blockers: 459 (25.2) | 692 (25.6) | 151 (21.9) | 0.25
- Beta blockers: 241 (13.3) | 831 (30.8) | 273 (39.6) | < 0.001
- Ace-inhibitors: 279 (15.3) | 421 (15.6) | 134 (19.4) | 0.031

#### Creatinine level, Umol/L
- 97.92 (19.35) | 100.76 (22.22) | 108.58 (25.08) | < 0.001

Values presented as mean (standard deviation) except as noted.

Abbreviations: SD, standard deviation; n, number; TIA, transient ischemic attack. P-values were calculated using log-transformed NT-proBNP levels for continuous variables and Chi-squared tests for categorical variables.
Table 2. Association of NT-proBNP with baseline cognitive function

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th>Cognitive tests (mean, SE)</th>
<th>Stroop, seconds</th>
<th>LDCT, digits coded</th>
<th>PLTi, pictures remembered</th>
<th>PLTd, pictures remembered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low N=1818</td>
<td>64.37 (1.46)</td>
<td>23.94 (0.41)</td>
<td>9.58 (0.11)</td>
<td>10.43 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Middle N=2698</td>
<td>64.13 (1.42)</td>
<td>23.54 (0.40)</td>
<td>9.52 (0.11)</td>
<td>10.40 (0.15)</td>
<td></td>
</tr>
<tr>
<td>High N=689</td>
<td>67.36 (1.63)</td>
<td>23.03 (0.46)</td>
<td>9.44 (0.12)</td>
<td>10.29 (0.17)</td>
<td></td>
</tr>
</tbody>
</table>

Data represent mean (standard error) score of each cognitive function test.

* P-values were calculated using the continuous value of log-transformed NT-proBNP levels.

Abbreviations: SE, standard error; n, number; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed.

Minimally adjusted model: adjusted for age, sex, country, education, apoe genotype, test version for LDCT and PLT.

Fully adjusted model: Minimally adjusted model + adjustments for history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index and serum creatinine.

Table 3 and Figure 1 show the association of NT-proBNP levels with changes in cognitive function during follow-up. Participants with higher NT-proBNP levels had a steeper cognitive decline on Stroop test, Letter-Digit Coding test and immediate and delayed Picture-Word Learning tests (all p-values < 0.001). Again, further adjustments for prevalent cardiovascular diseases or risk factors at baseline did not alter the observed associations (all p-values < 0.001). The association of NT-proBNP levels with cognitive decline from crude models did not materially differ from adjusted models.
**Table 3.** Association of NT-proBNP with cognitive decline during follow-up

<table>
<thead>
<tr>
<th>Cognitive tests (mean annual change, SE)</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low N=1818 Middle N=2698 High N=689</td>
</tr>
<tr>
<td></td>
<td>&lt;100 ng/L 100-450 ≥450 ng/L</td>
</tr>
<tr>
<td>Stroop, seconds</td>
<td></td>
</tr>
<tr>
<td>Minimally adjusted model</td>
<td>0.46 (0.11) 0.71 (0.09) 1.04 (0.26)</td>
</tr>
<tr>
<td>Fully adjusted model</td>
<td>0.47 (0.11) 0.72 (0.09) 1.04 (0.26)</td>
</tr>
<tr>
<td>LDCT, digits coded</td>
<td></td>
</tr>
<tr>
<td>Minimally adjusted model</td>
<td>-0.32 (0.02) -0.36 (0.02) -0.46 (0.04)</td>
</tr>
<tr>
<td>Fully adjusted model</td>
<td>-0.32 (0.02) -0.35 (0.02) -0.47 (0.04)</td>
</tr>
<tr>
<td>PLTi, pictures remembered</td>
<td></td>
</tr>
<tr>
<td>Minimally adjusted model</td>
<td>-0.00 (0.01) -0.03 (0.01) -0.05 (0.02)</td>
</tr>
<tr>
<td>Fully adjusted model</td>
<td>0.00 (0.00) -0.02 (0.01) -0.04 (0.02)</td>
</tr>
<tr>
<td>PLTd, pictures remembered</td>
<td></td>
</tr>
<tr>
<td>Minimally adjusted model</td>
<td>-0.05 (0.01) -0.06 (0.01) -0.10 (0.03)</td>
</tr>
<tr>
<td>Fully adjusted model</td>
<td>-0.03 (0.01) -0.05 (0.00) -0.10 (0.03)</td>
</tr>
</tbody>
</table>

Data represent mean annual change (standard error) in each cognitive function test. *P-values were calculated using the interaction term of time x log transformed NT-proBNP levels.

Abbreviations: SE, standard error; n, number; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed.

Minimally adjusted model: adjusted for age, sex, country, education, apoe genotype, treatment group, test version for LDCT and PLT. Fully adjusted model: Minimally adjusted model + adjustments for history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index and serum creatinine.

To further explore the influence of cardiovascular diseases and risk factors, we performed additional analyses in which we stratified for history of various cardiovascular diseases and risk factors, and tested for interaction. Figure 2 shows the association of NT-proBNP levels with cognitive decline, stratified by history of cardiovascular diseases and risk factors. There was no significant difference in change in cognitive function during follow-up between participants with and without cardiovascular diseases or risk factors, except for participants with a history of stroke and/or transient ischemic attack (TIA) and myocardial infarction. Participants with previous stroke and/or TIA had a less steep decline on Letter-Digit Coding test (p-value for interaction=0.003), while participants with previous myocardial infarction had a steeper decline on Letter-Digit Coding test (p-value for interaction=0.008). However, no such differences were observed for participants with previous stroke and/or TIA or myocardial infarction on
Figure 1. Association of NT-proBNP with cognitive decline during follow-up. Data represent mean score (95% confidence interval) of each cognitive test during follow-up, in each group of NT-proBNP. P-values were calculated using the interaction term of time x log transformed NT-proBNP levels. Adjustments were made for age, sex, country, education, apoE genotype and test version where appropriate.
any of the other cognitive tests.

Furthermore, we performed additional sensitivity analyses to investigate whether the association between NT-proBNP levels and cognitive function and decline could be affected by 1) participants taking pravastatin treatment during follow-up (n=2588); 2) participants with incident stroke and/or TIA during follow-up (n=355); 3) participants with incident myocardial infarction during follow-up (n=339); 4) participants with incident atrial fibrillation during follow-up (n=421); 5) participants with vascular events, including coronary heart disease death, nonfatal myocardial infarction, nonfatal and fatal stroke and/or TIA during follow-up (n=648); and 6) participants taking loop diuretics (n=588), beta blockers (n=1345) or ace-inhibitors (n=834) at baseline. Exclusion of these participants did not essentially change our results (data not shown).

Discussion

In this prospective cohort study including over 5000 men and women with mean age of 75 years, we showed that participants with higher NT-proBNP levels without advanced stages of clinical heart failure had worse cognitive function and steeper cognitive decline during a mean follow-up period of 3.2 years. These associations were independent of cardiovascular diseases and risk factors.

Our finding is in line with previous cross-sectional studies investigating the association of NT-proBNP and cognitive function\textsuperscript{1-5}. The Rancho Bernardo Study investigated the association in 950 community-dwelling adults of 60 years and older and found that higher NT-proBNP levels were associated with poor global and executive function, but not with cognitive flexibility\textsuperscript{1}. Another cross-sectional study including 1066 men and women aged 60-75 years with type 2 diabetes showed that higher NT-proBNP levels were weakly associated with lower general cognitive function\textsuperscript{2}. Furthermore, The Hoorn study found that baseline BNP was associated with worse processing speed, memory, attention and executive function. Besides, they observed that an increase of BNP over time was associated with reduced attention and executive function\textsuperscript{4}. So far only few other longitudinal studies investigated the association\textsuperscript{5}. In a prospective study, we previously found that at age 85, subjects in the highest tertile of NT-proBNP had a lower baseline MMSE score and a steeper decline in MMSE during a 5-year follow-up period (unpublished results). This is in line with the study performed by Kerola et al, who showed that BNP was associated with worse baseline score on MMSE, a higher decline of MMSE, and a higher incidence of dementia during a mean follow-up period of 5 years\textsuperscript{5}. To our knowledge, this is the first study
Figure 2. Association of NT-proBNP with cognitive decline during follow-up, stratified by cardiovascular diseases and risk factors. Data represent mean annual change (95% confidence interval) per 1 ng/L increase in log transformed NT-proBNP for each cognitive test, Stratified by cardiovascular diseases. Adjusted for age, sex, country, education, apoE genotype and test version where appropriate. P-values show p for interaction.
reporting on the association of NT-proBNP and cognitive function and decline in a large cohort of older participants without advanced stages of clinical heart failure at baseline and during follow-up.

Brain natriuretic peptide (BNP) and the biologically inactive N-terminal pro-brain natriuretic peptide are secreted by the ventricles of the heart in response to excessive stretching of cardiomyocytes. BNP has favorable physiological properties, including increased natriuresis and diuresis, relaxation of vascular smooth muscle cells and inhibition of the renin-angiotensin-aldosterone-axis, eventually causing a reduction in blood pressure and ventricular preload. Our results showed that higher NT-proBNP levels, and thus BNP as well, were associated with higher systolic blood pressure.

Different explanations can be proposed for the observed association of NT-proBNP with cognitive decline. First, NT-proBNP and cognitive decline may both reflect underlying cardiovascular damage and therefore stem from a common cause, rather than suggesting a causal relationship. Previous studies have shown that NT-proBNP levels have a prognostic value for the occurrence of cardiovascular events, such as myocardial infarction, atrial fibrillation, coronary heart disease, unstable angina, stroke and transient ischemic attack. This has also been demonstrated in subjects with elevated NT-proBNP levels, but without clinical heart failure. Furthermore, NT-proBNP levels provide predictive information for use of risk stratification in nonfatal cardiac events, stroke and mortality. Cardiovascular diseases are closely linked to cognitive dysfunction and dementia. This is in line with the finding that high NT-proBNP levels are associated with an increased prevalence of cardiovascular diseases and risk factors in the population under study. However, when adjusting and stratifying our analyses for cardiovascular diseases and risk factors, our results did not essentially change. Furthermore, excluding participants with incident myocardial infarction, stroke and/or TIA showed the same results. Nevertheless, we cannot totally rule out the possibility that unmeasured cardiovascular risk factors resulted in both increased NT-proBNP and cognitive decline. Second, impaired cardiac function may activate the renin-angiotensin system which in turn has been associated with cognitive decline. Recent evidence suggests that the renin-angiotensin system is important in the regulation of cerebral blood flow: it impairs cerebrovascular regulation and promotes oxidative stress and amyloid protein deposition. In line with this evidence, observational studies have shown that subjects receiving angiotensin receptor blockers have a lower decline in their cerebral perfusion and have a lower risk of developing dementia. Therefore, activation of the renin-angiotensin system might be a possible explanation on the observed association between higher NT-proBNP levels and cognitive decline. Since only a small number of participants used angiotensin receptor blockers in the population under study (n<100), we could not further
investigate this issue. Third, since natriuretic peptides have first been identified in porcine brain extract, one could hypothesize that NT-proBNP could have a direct effect in the brain. However, filtered by the blood brain barrier, the concentration of NT-proBNP in the brain is very low, if not undetectable\textsuperscript{31}. A fourth explanation might be that high NT-proBNP levels in subjects without advanced stages of heart failure indicate a suboptimal left ventricular functioning with subsequent decreased cardiac output and cerebral hypoperfusion\textsuperscript{8;15}. Cerebral hypoperfusion, which impairs the delivery of oxygen and nutrients to the brain, has been associated with cognitive dysfunction and dementia\textsuperscript{6-8}. In this scenario, high NT-proBNP levels could serve as a biomarker, reflecting suboptimal left ventricular function, which may result in cognitive decline. Although this explanation seems plausible, there is a need for interventional studies investigating the influence of improvement in cardiac function with its subsequent influence on cerebral perfusion, and eventually the prevention of cognitive decline in old age. Taken together, we favor the hypothesis that NT-proBNP could serve as a biomarker, reflecting suboptimal left ventricular function, which may result in cognitive decline. Major strengths of this study include the large sample size of over 5000 older participants and the repeated use of an extended standardized cognitive test battery to assess cognitive function over a mean follow-up period of 3.2 years. Furthermore, in contrast to previous studies, participants in our study had relatively preserved cardiac function, which gave us the opportunity to investigate the independent value of NT-proBNP in relation with cognitive function and decline. However, this study has several limitations. Our study population consisted of older participants at risk of cardiovascular diseases with relatively preserved cognitive function (MMSE $\geq$ 24 points), which might limit the extrapolation of our findings to a general population of older subjects. Furthermore, although participants with NYHA functional class III/IV were excluded from PROSPER, we might still have included participants with advanced stages of clinical heart failure but without ever being diagnosed with this condition. In addition, only information on heart failure hospitalization was available, which could have resulted in the inclusion of participants who developed clinical heart failure during follow-up, without being admitted to the hospital. However, excluding participants with NT-proBNP levels of $\geq$ 450 ng/L showed essentially the same results. In conclusion, higher NT-proBNP levels associate with worse cognitive function and steeper cognitive decline in older subjects without advanced stages of clinical heart failure. Although the exact underlying mechanism is unclear, NT-proBNP may serve as a biomarker of suboptimal left ventricular function, which through decreased cardiac output and cerebral hypoperfusion may result in cognitive decline.
Chapter 7 – Serum NT-proBNP and Risk of Cognitive Decline

References


Coll Cardiol 2002; 40(2):238-244.


