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ORIGINAL PAPER

Prognostic value of NT-pro-BNP and hs-CRP for risk stratification in primary care: results from the population-based DETECT study

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Abstract
Background There is continuous debate to the use of biomarkers in the general practitioners office and to what degree the established biomarkers N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and high-sensitive C-reactive protein (hs-CRP) might contribute to improved prediction of incident cardiovascular events.
Objective To evaluate the utility and 5-year predictive value of a single measurement of NT-pro-BNP and hs-CRP for incident cardiovascular events, and its added value beyond the contribution of conventional risk factors in primary care.
Methods Five year prospective longitudinal clinical epidemiological study in a nationwide sample of 4,775 primary care subjects (mean age 55.8 years, 62 % women) without coronary artery disease at baseline. Main outcome measures were incident major cardiovascular events and all-cause death.
Results During the 5 years of follow-up, 188 subjects (3.9 %) died or experienced a first major cardiovascular event. The addition of NT-pro-BNP, but not of hs-CRP to a prediction model with established cardiovascular risk factors improved the prediction of major cardiovascular events (increase in C statistic by 0.009; $p = 0.008$), and was associated with a significant improvement in net reclassification improvement (NRI = 23.6 %; $p = 0.003$).
Conclusion In a primary care setting, one single measurement of NT-pro-BNP, but not of hs-CRP significantly improves the prediction of incident cardiovascular events.

Keywords Biomarker · NT-pro-BNP · Hs-CRP · Risk stratification · Primary care

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Introduction

The assessment of risk factors for cardiovascular morbidity and mortality is essential for identifying subjects at risk in primary prevention. Established cardiovascular risk factors and global aggregated risk factor scores have so far failed to predict the risk of cardiovascular disease with sufficient accuracy in the community [1, 2]. Based on novel mechanistic insights into the biological processes underlying atherothrombosis [3], a variety of novel biomarkers has been proposed to relate to a person's risk for the

development of cardiovascular disease [4]. However, recent large-scale population-based studies provided conflicting results, whether novel biomarkers indeed add useful and clinically relevant information for risk prediction beyond standard risk factors [5–9].

Several studies published during the last years highlighted the significance and the prognostic impact of elevated concentrations of the biomarkers N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and high-sensitive C-reactive protein (hs-CRP) for patients with chronic heart failure [10, 11], acute coronary syndromes [12, 13], as well as for other structural heart diseases [10, 14]. However, in primary prevention, the role of hs-CRP and NT-pro-BNP is still not well defined, whereas the MORGAM biomarker project emphasizes the superior role of NT-pro-BNP out of 30 tested biomarkers [7], other population-based studies [9] did not reveal a relevant prognostic effect neither for hs-CRP, nor for measuring NT-pro-BNP in primary prevention.

Therefore, the aim of this analysis was to investigate whether the incorporation of NT-pro-BNP and hs-CRP into a model with established risk factors improved the prediction of incident cardiovascular events and death in a large population-based primary care sample of patients without a history of prior coronary artery disease.

Materials and methods

Study population

The "Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment" (DETECT) trial is a large multistage prospective-longitudinal study. The baseline study consisted of a nationwide representative sample of doctors with primary care functions (medical practitioners, general practitioners, general internists) [15] and included a total of 55,518 unselected consecutive patients recruited on two predefined half-day cutoff dates in 3,188 primary care offices in Germany. Subjects were included into the present study during a routine consultation with the primary physician for a good health examination or for treatment of an acute or chronic non-cardiac disease.

Within this study cohort, a representative partial sample of 7,519 subjects, randomly selected in 1,000 primary care offices, underwent additional laboratory tests and was evaluated for a 5-year time period [15]. This partial sample did not differ from the total study cohort with respect to the distribution of cardiovascular risk factors (Supplementary Table 1).

For inclusion into the present analysis, study participants had to be free of any history of prior myocardial infarction, known coronary artery disease, documented stroke, clinical signs of systolic or diastolic heart failure, and/or chronic kidney disease requiring hemodialysis at baseline. Further, subjects included needed to have complete data on clinical outcome as well as valid measures of NT-pro-BNP and hs-CRP plasma levels; this criterion mandated the exclusion of 104 patients. Combined, these inclusion criteria resulted in a total of 4,775 patients eligible for the analyses in this paper. Information about the baseline prevalence in the total sample has been published elsewhere [15].

The DETECT survey received the approval of the Ethics Committee of the Carl Gustav Carus Medical Faculty at the Technical University of Dresden (AZ EK149092003; Date 16.09.2003), and was registered at clinicaltrials.gov (NCT01076608).

Baseline examinations

The details of the standardized methods used in the DETECT study have been described previously [15]. In brief, all subjects signed an informed consent form and completed a self-report questionnaire, as well as a structured clinical interview and examination by the treating physician. The physicians also filled out a questionnaire documenting symptoms, diagnoses, treatments and health behavior of the individual subjects. In addition, a comprehensive laboratory assessment was performed. The venous blood samples were immediately frozen after collection until the time of the analysis. Plasma NT-pro-BNP levels were determined with a sandwich immunoassay on an ELECSYS2010 analyser (Roche diagnostics) and hs-CRP was assayed using latex-enhanced reagents (Siemens) on a BNProSpec analyser (Siemens).

For assessment of the established cardiovascular risk factors, the following definitions were applied: hypertension was defined as a systolic blood pressure $\geq$140 mmHg, a diastolic blood pressure $\geq$90 mmHg or treatment with antihypertensive medication [16]. NCEP guidelines [17] were applied for the diagnosis of dyslipidemia. Diabetes mellitus was defined by the use of antihyperglycemic medication or by a fasting plasma glucose level $\geq$126 mg/dL (7.0 mmol/L) [18], obesity was defined according to the WHO definition as body mass index (BMI) $\geq$30. Renal failure was defined as a glomerular filtration rate <60 mL/min/1.73 m^2, according to international guidelines.

Endpoints

State of health and medical history during follow-up were ascertained at conclusion of the trial in 2008. The following endpoints occurring in the 5-year follow-up period were documented: all-cause mortality, mortality of cardiovascular cause, occurrence of a myocardial infarction,

and manifestation of coronary artery disease as evidenced by the necessity for coronary revascularization by either bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). All information on endpoints was determined by a standardized assessment form by the primary care physician and/or by the institution, in which the patient was previously treated. Further information from the cause of death registry was taken into account. For prediction and reclassification analyses, a combined endpoint of "major cardiovascular events" (MACE) was used including death from cardiovascular causes, non-fatal myocardial infarction and necessity for coronary revascularization by CABG surgery or PCI.

Statistical analyses

The association of NT-pro-BNP and hs-CRP with different outcomes were investigated with the use of Cox proportional hazards regression. Besides crude analyses, hazard ratios were adjusted for age, gender and body mass index for established influences on the level of biomarkers [19]. Hazard ratios were additionally adjusted for established cardiovascular risk factors like systolic and diastolic blood pressure, hyperlipidemia, diabetes, smoking status, waist circumference, renal failure, and depression. The proportional hazard assumptions were confirmed by Schoenfeld residuals. The association of the biomarkers and outcomes were evaluated in a continuous regression model according to a one standard deviation (SD) increase in biomarker levels as well as by a cutoff point that was identified to achieve optimal discrimination for each endpoint. The optimal cutoff of NT-pro-BNP and hs-CRP values was determined by selecting the maximum of sensitivity and specificity in ROC analyses [20] and was specifically calculated for each endpoint. The integrated discrimination improvement measure [21] was also considered for evaluating the incremental value of biomarkers besides established cardiovascular risk factors. Estimates of the *C* statistic after Cox regression models (with 95 % confidence intervals) [22] for conventional cardiovascular risk factors, with and without the biomarkers, were calculated to assess model discrimination. We also investigated whether the addition of the combination of the two biomarkers improved the discrimination of the models [23].

In addition, we evaluated the ability of biomarkers to reclassify risk, following methods suggested previously [6, 9]. Using multivariable risk models with the clinical covariates noted above, participants were initially classified as at low, intermediate, or high risk if their predicted 10-year risk of a coronary event by Framingham Score was >6 %, 6 % to >20 %, or 20 % or greater, respectively. Subjects were then reclassified into different categories according to the addition of the biomarker data. Calibration is also an important feature for assessing the accuracy of risk prediction and was assessed by the Hosmer–Lemeshow test statistics after fitting the prediction models. Quantile–quantile plots were applied for displaying the change in estimated risk by adding the biomarker Nt-pro-BNP. Standard errors and confidence intervals were estimated by the robust Huber-White sandwich covariance matrix estimator. *P* values of >0.05 from two-sided test were considered to indicate statistical significance. All statistical analyses were conducted with the use of STATA 10.

Results

A total of 4,775 participants with no previous history of cardiovascular disease at baseline were included into the analysis. The baseline characteristics of the study cohort are illustrated in Table 1. Consistent with the age and gender distribution in primary care in Germany, the mean age of participants at baseline was 55.8 years (SD 13.8 years; range 18–95 years) and 2,957 participants (61.9 %) were women. 20.6 % received beta-blockers and 16.4 % of the participants received ACE-inhibitor (ACI)/Angiotensin-receptor-blocker (ARB) therapy. Hyperlipidemia was treated in 10.7 % of the subjects by statins.

During the follow-up period of 5 years, 107 participants (2.2 %) died and 98 of the 4,775 participants (2.1 %) experienced an incident major cardiovascular event (MACE 17 = cardiovascular death, 30 = myocardial infarction, 51 = revascularization by PCI or CABG surgery). The MACE rate in the 1 year of follow-up was 22, and in the second year 25. All-cause-mortality rates were: 17 deaths in the first year, and 25 deaths in the second year.

Prediction of cardiovascular events using biomarkers

Elevated NT-pro-BNP plasma levels at baseline were associated with increased 5-year hazard ratios for all-cause mortality (HR 5.02; CI 3.26–7.72; $p < 0.0001$) (Table 2) and for incident major cardiovascular events (HR 4.38; CI 2.82–6.80; $p < 0.0001$), consisting of cardiovascular events and mortality due to myocardial infarction or sudden cardiac death (SCD), estimated by crude or adjusted statistical models. Increased levels of hs-CRP significantly increased hazard ratios for death from all-cause mortality as well as for major cardiovascular events (Table 2). This association was not affected by the presence or absence of established cardiovascular risk factors, like arterial hypertension (Supplementary Table 2a), hyperlipidemia (Supplementary Table 2b), or diabetes mellitus (Supplementary Table 2c), and the

Table 1 Baseline characteristics of the study population ($n = 4,775$)

Characteristics	Value[a]
Age, mean (SD), years	55.8 (13.8)
Female	2,957 (61.9 %)
Hypertension, (*n*)	1,665 (34.9 %)
Systolic blood pressure, mean (SD), mmHg ($n = 4,669$)	131.7 (18.1)
Diastolic blood pressure, mean (SD), mmHg ($n = 4,669$)	80.1 (9.7)
Antihypertensive treatment, (*n*)	1,472 (32.4 %)
ACE-I or ARB, (*n*)	744 (16.4 %)
Beta-blocker, (*n*)	936 (20.6 %)
Calcium channel blocker, (*n*)	462 (10.2 %)
Diuretics, (*n*)	565 (12.4 %)
Diabetes mellitus, (*n*)	592 (12.4 %)
Fasting plasma glucose, mean (SD), mg/dL ($n = 4,773$)	99.1 (32.4)
Insulin treatment, (*n*)	164 (3.6 %)
Oral treatment, (*n*)	378 (8.3 %)
Hyperlipidemia, (*n*)	1,328 (27.8 %)
Statins, (*n*)	485 (10.7 %)
Other lipid lowering drugs, (*n*)	125 (2.8 %)
Total cholesterol, mean (SD), mg/dL ($n = 4,739$)	225.5 (42.0)
HDL cholesterol, mean (SD), mg/dL ($n = 4,739$)	55.8 (18.6)
LDL cholesterol, mean (SD), mg/dL ($n = 4,739$)	129.0 (33.2)
Current smoker ($n = 4,612$), (*n*)	949 (21.5 %)
Ex-smoker ($n = 4,612$), (*n*)	1,088 (24.7 %)
Family history of CAD ($n = 4,623$), (*n*)	682 (14.8 %)
Hip to waist ratio, mean (SD) ($n = 4,511$)	1.13 (0.13)
Body mass index, mean (SD), kg/m^2 ($n = 4,623$)	26.9 (4.8)
Framingham risk score (%), mean (SD)	10.4 (10.6)
SCORE risk (%), mean (SD)	2.64 (4.08)
Biomarkers	
hs-CRP	
Mean (SD), (mg/L)	4.3 (6.9)
Interquartile-range (mg/L)	0.96–4.42
NT-pro-BNP	
Mean (SD), (pg/mL)	122.2 (303.8)
Interquartile-range (pg/mL)	29.04–117.3

CAD coronary artery disease, *hs-CRP* high-sensitive C-reactive protein, *n* number, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide, *SD* standard deviation, *ACE-I* ACE-Inhibitors, *ARB* Angiotensin-receptor-blocker

[a] All percentages refer to number of subjects with existing data

subgroup of patients with a lower Framingham risk score demonstrated a stronger association than the higher risk group (Supplementary Table 2d).

The combination of both biomarkers, NT-pro-BNP and hs-CRP, was associated with a further increase in hazard ratios for MACE (HR 9.72; CI 3.57–26.45; Fig. 1). Interestingly, the probability for both, MACE as well as all-cause mortality, was higher (MACE: HR 5.71; CI 1.85–17.61) for the constellation of elevated NT-pro-BNP and low hs-CRP compared with the constellation of elevated hs-CRP and low NT-pro-BNP (MACE: HR 3.73; CI 1.40–9.94; Fig. 1).

Added value of the biomarkers NT-pro-BNP and hs-CRP

Discrimination

The *C* statistics for Cox regression models increased significantly for the prediction of major cardiovascular events, when NT-pro-BNP plasma levels were separately incorporated into a model with the established cardiovascular risk factors (Table 3). In contrast, the added prognostic value of hs-CRP with respect to predicting MACE was small, and the combination of NT-pro-BNP and hs-CRP

Table 2 Hazard ratios for death by all causes and for major adverse cardiovascular events (MACE) according to biomarker levels within the whole study cohort ($n = 4{,}775$)

	Death by all causes		MACE	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
NT-pro-BNP				
1-SD increase, crude	1.17 (1.13–1.21)	<0.001	1.12 (1.06–1.18)	<0.001
≥Cutoff, crude	5.02 (3.26–7.72)	<0.001	4.38 (2.82–6.80)	<0.001
1-SD increase, adjusted[a]	1.10 (1.07–1.13)	<0.001	1.06 (1.00–1.13)	0.036
≥Cutoff, adjusted[b]	2.58 (1.65–4.04)	<0.001	2.92 (1.90–4.48)	<0.001
1-SD increase, adjusted[b]	1.10 (1.07–1.13)	<0.001	1.07 (1.01–1.14)	0.020
≥Cutoff, adjusted[b]	2.53 (1.62–3.96)	<0.001	2.97 (1.94–4.56)	<0.001
hs-CRP				
1-SD increase, crude	1.25 (1.11–1.40)	<0.001	1.13 (0.96–1.33)	0.134
≥Cutoff, crude	2.42 (1.52–3.87)	<0.001	3.08 (1.73–5.47)	<0.001
1-SD increase, adjusted[a]	1.23 (1.09–1.38)	0.001	1.11 (0.95–1.29)	0.186
≥Cutoff, adjusted[a]	1.91 (1.17–3.13)	0.010	2.46 (1.39–4.33)	0.002
1-SD increase, adjusted[b]	1.22 (1.08–1.39)	0.002	1.11 (0.96–1.29)	0.170
≥Cutoff, adjusted[b]	1.82 (1.10–2.99)	0.019	2.30 (1.31–4.04)	0.004

CI Confidence interval, *HR* Hazard-ratio, *hs-CRP* high-sensitive C-reactive protein, *MACE* major adverse cardiovascular event, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide, *SD* standard deviation

Optimal cutoff values: *NT-pro-BNP* all-cause-death (>85.8 pg/ml); major adverse cardiovascular event (>121.9 pg/mL), *hs-CRP* all-cause-death (>1.4 mg/l); major adverse cardiovascular event (>1.47 mg/L)

[a] Data were adjusted for the following variables: age at baseline (continuous), gender (binary), body mass index (continuous), creatinine (continuous)

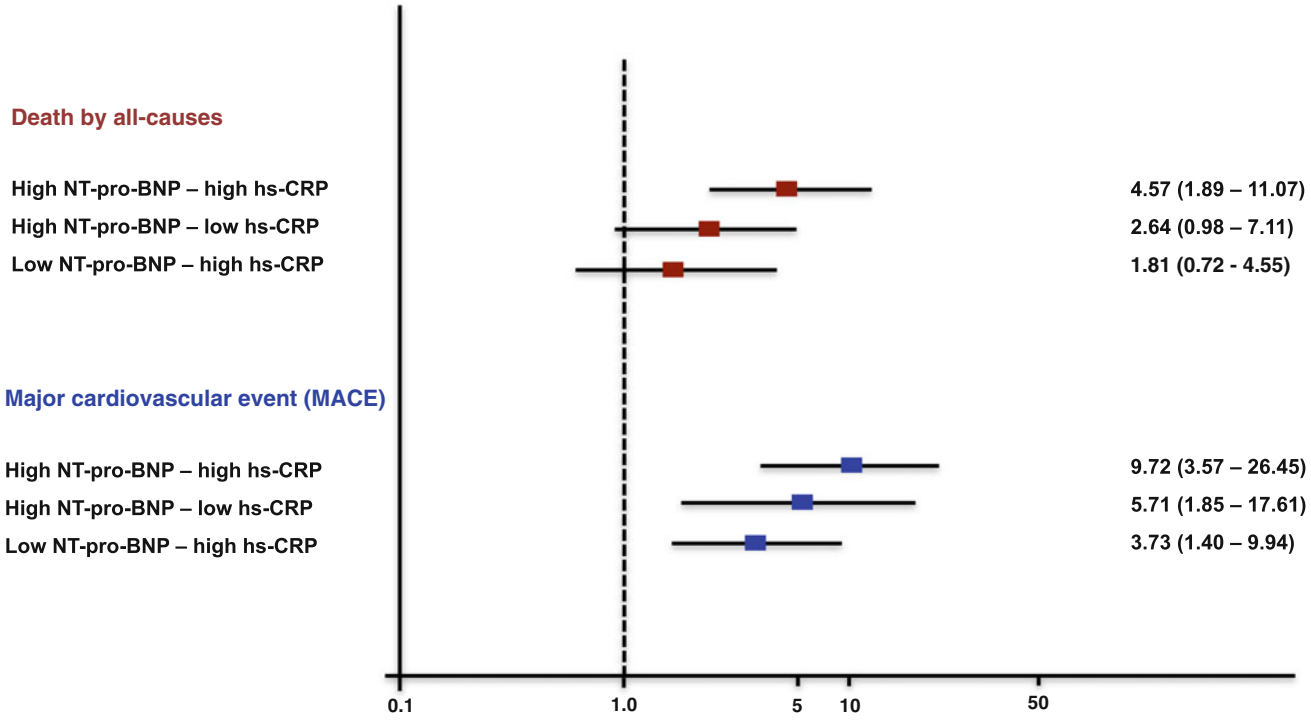
[b] Data were adjusted for the following variables: age at baseline (continuous), gender (binary), body mass index (continuous), smoking status (binary), waist circumference (continuous), creatinine (continuous), systolic blood pressure (continuous), diastolic blood pressure (continuous), hyperlipidemia (binary), diabetes (binary), depression (binary)

resulted in only a small, non-significant increase in *C* statistics ($C = 0.819$; increase of $C = 0.003$; $p = 0.153$; Table 3).

Reclassification

Reclassification represents a more clinically informative way of quantifying the added value of adding NT-pro-BNP and hs-CRP to conventional cardiovascular risk factors (24). Therefore, we assessed the number of participants reclassified and calculated the net reclassification improvement (NRI) and discrimination improvement (IDI) on top of the Framingham 10-year risk prediction of a major cardiovascular event. As summarized in Table 4, net reclassification significantly ($p = 0.003$) improved for major cardiovascular events, when NT-pro-BNP was incorporated into the risk model. Likewise, the integrated discrimination index was significantly improved ($p = 0.001$). In fact, of the 98 subjects, who suffered a major cardiovascular event, reclassification was more accurate in 39 subjects (39.8 %), whereas it became less accurate in 20 subjects (20.4 %), when NT-pro-BNP was included in the risk prediction model. On the other hand, among the subjects who did not suffer a major cardiovascular event, 478 subjects (10.2 %) were reclassified in a lower risk category and 376 (8.0 %) were reclassified in a higher risk category. Overall, the net improvement in reclassification was estimated at 23.6 % ($p = 0.003$), indicating that every 4th participant would be reclassified after adding a single NT-pro-BNP plasma level measurement at baseline to conventional risk factors for prediction of major cardiovascular events in primary prevention. Adding hs-CRP to NT-pro-BNP plasma levels into the risk prediction model did not significantly alter net reclassification indices as compared to using NT-pro-BNP plasma levels alone (NRI 25.2 %, $p = 0.001$ for the combination compared to NRI 23.6 %, $p = 0.001$ for NT-pro-BNP alone) (Table 4).

Net reclassification indices were not calculated for all-cause mortality, since there are no clinical risk categories for all-cause mortality. The change in estimated risk is shown by the quantile–quantile plot in Fig. 2, when NT-pro-BNP was included in the prediction model (Fig. 2) for MACE. The inclusion of NT-pro-BNP in risk prediction resulted in a higher estimated risk. The prediction model was well calibrated indicating a close agreement of the predicted probabilities with the actual endpoint.



(*) Optimal cut-off values:
NT-pro-BNP: All-cause-death (>85.8 pg/ml); Major adverse cardiovascular event (>121.9 pg/mL)
hs-CRP: All-cause-death (>1.4 mg/l); Major adverse cardiovascular event (>1.47 mg/L)

Fig. 1 Hazard ratios and 95 % confidence intervals for the endpoints "All-cause mortality" and "Major cardiovascular events (MACE)", according to combinations of biomarker levels (*asterisk*)

Table 3 *C* Statistics for Cox regression models predicting death from all causes and major cardiovascular events (MACE)

	Death by all causes		MACE	
	C statistic	*p* value	*C* statistic	*p* value
Established risk factors[a]	0.820	Reference model	0.810	Reference model
Established risk factors[a] plus NT-pro-BNP	0.823	0.044	0.816	0.003
Established risk factors[a] plus hs-CRP	0.826	0.014	0.812	0.256
Established risk factors[a] plus NT-pro-BNP and hs-CRP	0.829	0.023	0.819	0.008
Estimated difference with the addition of NT-pro-BNP and hs-CRP	0.010	0.023	0.009	0.008

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *hs-CRP* high sensitive C-reactive protein, *MACE* major adverse cardiovascular event, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide

[a] Established risk factors: systolic and diastolic blood pressure, smoking status, hyperlipidemia, diabetes mellitus, body mass index

Discussion

In this large sample of primary care subjects without evidence of major cardiovascular disease at baseline, the incorporation of the biomarker NT-pro-BNP into a model with established traditional risk factors substantially improved risk stratification for incident major cardiovascular events and death over a 5-year period. This effect is evidenced by a significant increase in the *C* statistics for Cox regression models and a significant improvement in net reclassification.

A variety of biomarkers has been proposed to reflect the complex biology underlying atherothrombosis, which encompasses hemostasis, thrombosis, inflammation, endothelial dysfunction, plaque instability and neurohumoral activation [9, 24]. However, when prospectively tested in large-scale community-based studies to predict cardiovascular events in primary prevention, biomarkers from multiple, biologically distinct pathways did add only moderate, if any, significant additional information over and above conventional risk factor assessment of individual subjects [5, 6]. However, even though only a marginal utility for

Table 4 Added predictive validity of NT-pro-BNP and/or hs-CRP on top of established cardiovascular risk factors compared to a model with only established cardiovascular risk factors regarding incident MACE within the whole study cohort

	Higher risk classification n (%)	Lower risk classification n (%)	Net gain% (*p* value)	NRI % (*p* value)	IDI[a] % (*p* value)
NT-pro-BNP					
Subjects ($n = 4{,}775$)				23.57 (0.003)	1.46 (0.001)
Event	39 (39.8)	20 (20.4)	19.39 (0.006)		
No Event	376 (8.0)	478 (10.2)	−2.18 (<0.0001)		
hs-CRP					
Subjects ($n = 4{,}775$)				4.86 (0.197)	0.06 (0.340)
Event	18 (18.4)	13 (13.3)	5.10 (0.185)		
No Event	251 (5.4)	262 (5.6)	−0.24 (0.313)		
NT-pro-BNP and hs-CRP					
Subjects ($n = 4{,}775$)				25.22 (0.001)	1.46 (0.001)
Event	37 (37.8)	15 (15.3)	22.45 (0.001)		
No Event	390 (8.3)	520 (11.1)	−2.78 (<0.0001)		

Established risk factors: age, gender, systolic and diastolic blood pressure, smoking status, hyperlipidemia, diabetes mellitus, body mass index

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide, *hs-CRP* high sensitive C-reactive protein, *IDI* integrated discrimination improvement, *NRI* net reclassification improvement

[a] IDI: integrated discrimination improvement = difference of averaged improvement in sensitivity and averaged increase in 1-specificity

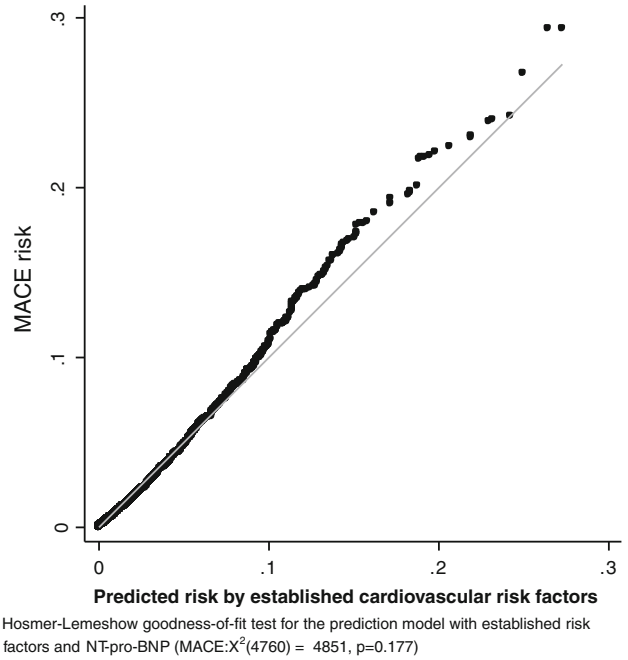


Fig. 2 Quantile–quantile plots of the estimated 5-year risk for "Major cardiovascular event (MACE)" by established risk factors and by NT-pro-BNP (*dotted line*)

multiple novel biomarkers was described, NT-pro-BNP and hs-CRP emerged as the most useful predictors of cardiovascular events in primary prevention [5–7, 9, 25]. Therefore, in the present study, we focussed on measuring NT-pro-BNP and hs-CRP plasma levels. Furthermore, to our knowledge, the present study is the first population-based study evaluating the predictive value of biomarkers directly in an unselected general practitioner study cohort, where simple, time-efficient, but also maximal by effective tools are necessary for individual cardiovascular risk assessment. Our results demonstrate that the addition of NT-pro-BNP levels to conventional risk stratification substantially improves the prediction of incident major cardiovascular events in primary prevention. These data corroborate recently published findings in other primary prevention cohorts with a comparable risk profile as we observed in the DETECT cohort [7].

Importantly, in the present study, the net improvement in reclassification of approximately one quarter of all subjects was observed on top of an already rather high accuracy of conventional risk factors to predict the risk for major cardiovascular events as estimated by a *C* statistics of 0.810, which is considerably higher than the *C* statistics reported in previous studies ranging from 0.69 to 0.76 [5, 6, 9]. These differences in the accuracy of risk prediction by conventional risk factors seem to be well explained by the different study populations. Zethelius et al. [9] included a rather small study cohort of only men with a very narrow age range of 67–75 years, thereby reducing the *C* statistics for Cox regression models to 0.688. In the study cohort analyzed by Melander et al. [6], a possible preselection bias cannot be excluded due to the fact that the Malmö Diet and Cancer study only consisted of voluntary participants. It was actually shown that the cancer incidence as well as the overall mortality in this study population was lower than in the non-participants, suggesting that the participating study

cohort was healthier [26]. In contrast to these general population-based studies, the DETECT sample in the present study is unique in several ways: it is based on a nationwide representative random sample of primary care patients, sampled in 2003 and, thus, reflects a more appropriate, generalizable snapshot of current primary prevention subjects in the field of general practitioners medicine.

Our observation that NT-pro-BNP levels are superior to hs-CRP levels to provide incremental predictive information with respect to incident major cardiovascular events is in line with the results of previously published smaller studies in a geographically defined population [27], in a primary prevention cohort of elderly men [28], as well as in a hypertensive population without pre-existing cardiovascular disease [29]. Similar results were observed in the field of secondary prevention [30]. However, the results of the present study should not be construed as implying a limited usefulness of hs-CRP to guide statin therapy in primary prevention, as documented by the profound risk reduction by rosuvastatin in a primary prevention cohort with hs-CRP levels >2 mg/L in the JUPITER trial [31].

While NT-pro-BNP is a well established diagnostic and prognostic biomarker in patients with heart failure [32], a variety of additional cardiovascular pathological conditions are associated with moderately elevated serum levels of NT-pro-BNP: myocardial ischemia (even if only transient), left ventricular hypertrophy, left ventricular diastolic dysfunction, right ventricular pressure overload, and increased global left ventricular strain or wall stress. Thus, it is very likely that the prognostic significance of NT-pro-BNP in the present study may reflect the presence of subclinical cardiovascular disease. Indeed, a recent study in subjects without any traditional cardiovascular risk factors and echocardiographic exclusion of any structural cardiac abnormalities failed to demonstrate a prognostic role for NT-pro-BNP serum levels, although the size of the study population was rather small with 703 subjects [33].

Some limitations of our analysis merit discussion. Albeit rather small, the relative number of cardiovascular events in the present study with a 5-year follow-up period is essentially identical to data from recently published European population-based studies in primary prevention [7], suggesting the usefulness of the DETECT cohort for cardiovascular risk estimation in a primary prevention population free of coronary artery disease. Second, according to a recent recommendation [34], we restricted our combined endpoint to the occurrence of myocardial infarction, coronary revascularization by PCI or CABG and cardiovascular mortality due to sudden cardiac death or fatal myocardial infarction. We do believe that this is an appropriate choice given that this combined endpoint has not only been used in previous risk stratifying models [8], but is also a universally accepted endpoint used in major cardiovascular clinical trials evaluating pharmacological interventions for primary prevention. We purposely omitted onset of congestive heart failure as an endpoint, because of the lack of strict diagnostic criteria. Third, follow-up time was 5 years in the present study, whereas previous community-based studies reported on follow-up times ranging from 7 to 12 years [5, 6, 9]. Given the rapid developments in pharmacological therapies emerging in primary prevention over the last decade, we felt it to be important to limit the follow-up observation period to avoid potential confounding effects of changing clinical practice in primary prevention strategies, e.g., like the emergence of ACE-inhibitor/ARB therapy being used across a broad range of cardiovascular risk since the late 90s and early 2000. Moreover, a 3- to 5-year follow-up time has been typically used in major cardiovascular clinical trials evaluating interventions for primary prevention [35].

Thus, if the addition of biomarkers to more accurately predict the risk for incident major adverse cardiovascular events will ultimately translate into a clinically significant benefit, cardiovascular endpoint trials will have to evaluate a potential benefit from individualized specific therapies based on biomarker-guided risk stratification, as has been exemplified by the JUPITER trial [31].

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