N-terminal pro-brain natriuretic peptide, but not high sensitivity C-reactive protein, improves cardiovascular risk prediction in the general population

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Aim Serum N-terminal pro-brain natriuretic peptide (NT-proBNP), high sensitivity (hs)-C-reactive protein, and urine albumin/creatinine ratio (UACR) are cardiovascular (CV) risk markers in the general population. The aim of this study was to determine whether they predicted CV events independently of established CV risk factors and whether they did so in an additive fashion.

Methods and results In a population-based sample of 2656 individuals, 41, 51, 61, and 71 years old, we measured UACR, serum NT-proBNP, hs-C-reactive protein, insulin, lipids and plasma glucose, clinic blood pressures, body composition, left ventricular (LV) mass index, and ejection fraction (EF) by echocardiography and pulse wave velocity. During the following 9.4 years, the combined CV endpoint (CEP) of CV death (136), non-fatal stroke, or non-fatal myocardial infarction occurred in 219 subjects. After adjustment for established CV risk factors using Cox-regression analyses, CEP and CV death were predicted by log(NT-proBNP)/SD [hazard ratio (HR) = 1.58 and HR = 1.80, both P < 0.001] and by log(UACR)/SD (HR = 1.44 and HR = 1.52, both P < 0.001) in an additive fashion, but not by log(hs-C-reactive protein)/SD (HR = 1.17, P = 0.06 and HR = 1.13, NS). CV risk functions were constructed on the basis of Cox-regression analyses. Inclusion of NT-proBNP and UACR did not increase the area under the receiver-operating characteristic plots.

Conclusion Serum NT-proBNP and UACR, but not hs-C-reactive protein, predicted CV events after adjustment for established CV risk factors including LV EF and relative wall thickness. However, more studies in relevant subgroups are needed before NT-proBNP and UACR can be recommended for risk prediction in the general population to select subjects for primary prevention.

Introduction

Studies of risk factors for future morbidity and mortality in the general population are important for identification of groups likely to benefit from risk factor intervention. Classical risk scores relying on age, gender, blood pressure, and smoking have proved useful, but their predictive value for the individual is not accurate and therefore not very useful clinically.1–3 Novel cardiovascular (CV) risk markers like high sensitivity (hs)-C-reactive protein,4,5 urine albumin/creatinine ratio (UACR),6 brain natriuretic peptide (BNP),7 and N-terminal (t) proBNP8 have all been demonstrated to predict CV events in the general population, but previous studies have not addressed their importance in a comprehensive context including traditional CV risk factors and known markers of CV damage. Recently, we showed in a general population sample,9,10 that hs-C-reactive protein was primarily related to metabolic CV risk factors whereas N-terminal pro-brain natriuretic peptide (NT-proBNP) was primarily related to haemodynamic CV risk factors and UACR related to both haemodynamic and metabolic CV risk factors. Thus, in the theory, the novel markers could add different information to the traditional CV risk factors and thereby complement each other.

Therefore, the aim of the present study was to investigate whether these three new emerging CV risk markers predicted CV death, non-fatal stroke, and non-fatal myocardial infarction independently of established CV risk factors and

GENERAL POPULATION

KEYWORDS
N-terminal pro-brain natriuretic peptide;
High sensitivity C-reactive protein;
Albuminuria;
Cardiovascular risk factors;
Population survey;
Left ventricular hypertrophy;
Left ventricular systolic function;
Pulse wave velocity;
Prognosis

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markers of CV damage in the general population, and whether they carried additive prognostic information.

**Methods**

**Study design**

In 1982–84, 4807 individuals aged 30, 40, 50, or 60 years, randomly selected from the population near Glostrup University Hospital, were invited to participate in a population survey (82.6% participated). In 1993–94, 3785 former participants were re-invited and 2656 (70.2%) accepted and participated in the following investigations. At the same day, an echocardiogram was performed, aortic pulse wave velocity (PWV) was measured, blood samples were obtained for analysis of plasma glucose, serum insulin, and lipid profile, serum NT-proBNP, serum hs-C-reactive protein, and a morning urine sample was collected to calculate UACR. All three new risk markers were available in 2502 subjects. A trained nurse measured anthropometric characteristic. Waist to hip ratio was calculated from measurements of the widest circumferences located between the lower rib and the iliac crest and around the hips.

The participants completed a self-administered questionnaire concerning their past and current medical history, intake of medication, and lifestyle. Based on self-reported physical activity, the subjects were divided in three groups: Subjects without physical activity (21%), subjects with light physical activity (daily walking, frequently bicycling or less than half an hour sport activity each day) (57%), and subjects participating in sport activities more than half an hour each day (22%); 46.2% (1225) were daily smokers and 27.5% (729) ex-smokers. Daily alcohol consumption was registered as none (14%), 1–6 cl (74%), or more than 6 cl strong alcohol (12%). The study was approved by the Local Ethics Committee and the subjects gave informed consent.

After a median of 9.4 years, a complete follow-up regarding death was obtained through information from the Civil Registration System until October 2003. Information on CV mortality was obtained from blinded classification of death certificates and information on hospitalization was recorded from The Danish National Health Register, the data from which have previously been validated. A composite CV endpoint (CEP) of CV death, non-fatal myocardial infarction, and non-fatal stroke were chosen as primary endpoint because prior occurrences of these endpoints were recorded at baseline. Prior hospitalizations for angina and heart failure were not recorded at baseline.

**Echocardiography**

Studies were performed using M-mode and two-dimensional echocardiograms and read by one experienced physician blinded for all other information. Left ventricular (LV) internal dimension and wall thickness were measured at end-diastole and end-systole following American Society of Echocardiography recommendations and endocardial ejection fraction (EF) was calculated. End-diastolic LV dimensions were used to calculate LV mass, which was corrected for body size by dividing with body surface area.

**Pulse wave velocity**

Two transducers connected to a printer were placed over the common carotid artery and the femoral artery. PWV was calculated as the distance between the two transducers measured on the surface divided by the calculated time delay for the pulse wave between the two transducers.

**Blood pressure**

Office BP and heart rate were measured sitting after 5 min of rest with the participants arm at the level of sternum with a random zero mercury sphygmomanometer and the mean of two measurements was reported. Heart rate was counted over 15 s.

**Assays**

Urine albumin concentration was determined by standard methods using a turbidimetric method (Hitachi 717 analyzer, Roche Diagnostics, Mannheim) on a single urine specimen taken in the morning. Urine creatinine was analysed using the Jaffé reaction without deproteinizing and then quantified by a photometric method (Hitachi 717 analyzer, Roche Diagnostics). UACR was calculated.

Serum hs-C-reactive protein concentration was determined using a particle-enhanced immunoturbidimetry assay (Roche/Hitachi) range 0.1–20 mg/L and lowest detection limit 0.03 mg/L. Serum NT-proBNP concentration was determined using Elecsys proBNP sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics). The analytical range was 5.1–34927 pg/mL. Between-assay coefficients of variation in low and high ranges of NT-proBNP are reported to be 4.8 and 2.7%. Serum was frozen immediately at −20 °C to be examined in July 2003. We have previously published data showing that hs-C-reactive protein as well as NT-proBNP appear to be stable in the frozen samples.

**Statistics**

Statistical analyses were performed using SPSS 12.0 (SPSS, Chicago, IL, USA) software. Data are presented as median and inter-quartile range (IQR) for continuous variables and proportions for categorical variables. Variables with skewed distributions were normalized by log10 transformation. The associations between the three new risk markers were tested using multiple regression analyses adjusting for age, gender, and prior stroke or myocardial infarction. Hazard ratios (HRs) and their 95% confidence intervals for CV events were assessed using Cox-regression analysis with stepwise adjustment with a threshold criteria of 5% for potential confounders [i.e. history of diabetes, prior stroke or myocardial infarction, intake of any CV medication, age and gender, lifestyle (daily exercise, alcohol consumption, and smoking status), body composition (waist circumference), metabolic CV risk factors (glucose, insulin, total cholesterol, high- (HDL) and low-density lipoprotein (LDL) cholesterol, triglyceride), haemodynamic CV risk factors (heart rate, office BP) and subclinical CV damage (LV mass index, LVEF, and PWV)]. We used a stepwise adjustment to observe whether one of the new risk markers was related closely in particular to certain CV risk factors. All variables were tested for linearity, proportional hazards assumption, and interaction with age and gender demonstrating that all three novel risk markers had to be logarithmic transformed before included in Cox-regression analyses.

To ensure that predictors included by chance in our Cox models did not influence the main results, we repeated the analyses using forced Cox models with traditional CV risk factors known to be important for the outcome (history of diabetes, prior stroke or myocardial infarction, intake of any CV medication, age, gender, smoking, total cholesterol, systolic BP, and heart rate).

To compare HRs, we repeated Cox-regression analyses after standardizing the variables by dividing with the standard deviations of the transformed variables. Age above or below the median age, gender, smoking and history of diabetes, prior stroke or myocardial infarction were tested for potential modulation of the effect of UACR, hs-C-reactive protein, and NT-proBNP on CV events by formal interaction tests. Due to large gender, differences in UACR and NT-proBNP median values were calculated for men and women separately. Interaction tests were not adjusted. Finally, we used SAS software, version 9.1 (SAS Institute, Cary, NC, USA) to calculate the 10-year absolute risk of CV death or CEP at different levels of NT-proBNP, hs-C-reactive protein, and UACR.

To test whether log(UACR), log(hs-C-reactive protein), or log(NT-proBNP) increased CV risk prediction significantly, we compared the best Cox-regression models with and without the new risk marker tested using the likelihood ratio-test in the 2502 subjects with all three risk markers available. Based on these Cox-regression
models, we calculated coefficients and constants to construct risk functions calculating prognostic indexes for the CEP as well as CV death (Appendix 1). These risk functions were compared using receiver-operating characteristic (ROC) plots.17 Two-tailed

Results

Prognostic value of UACR, high sensitivity C-reactive protein, and Nt-proBNP

Approximately half of the population consisted of men (50.3%), 45% were 61 or 71 years, 46% were current smokers, 2.8% (74 subjects) had diabetes, and 5.1% (135 subjects) had prior stroke or myocardial infarction. During the median follow-up of 9.4 (0.17–10.3) years, 219 subjects experienced a CEP. In 136 subjects, the first endpoint was CV death, in 81 fatal or non-fatal myocardial infarction. Adjusted for age, gender and prior stroke or myocardial infarction, log(UACR) was related to log(Nt-proBNP) (β = 0.16, P < 0.001), but only weakly to log(hs-C-reactive protein) (β = 0.06, P = 0.01), and log(Nt-proBNP) and log(hs-C-reactive protein) were unrelated (β = 0.03, P = 0.12). The new, emerging CV risk markers as well as the established CV risk factors listed in Table 1, except body mass index, all predicted CEP and CV death in univariable Cox-regression analyses (data not shown). In univariable Cox-regression analyses using dichotomized variables, subjects with hs-C-reactive protein [HR = 2.1 (1.6–2.8) and HR = 2.3 (1.6–3.3)], UACR [HR = 3.0 (2.2–4.0) and HR = 3.2 (2.2–4.8)] or Nt-proBNP [HR = 3.3 (2.4–4.5) and HR = 5.9 (3.7–9.5), all P < 0.001] above the median values had a two- to six-fold higher risk of experiencing either CEP or CV death compared to a 1.5- to 3.5-fold risk increase in subjects with either serum cholesterol, plasma glucose, or systolic BP above the median values.

The effect of log/(hs-C-reactive protein) on CEP and CV death was significantly modulated by gender (P = 0.02 and P = 0.048), but not by age (P = 0.38 and P = 0.24), with almost twice as high HRs in men [HR = 3.4 (2.4–4.7) and HR = 3.9 (2.5–6.0) for a 10-fold increase in hs-C-reactive protein, both P < 0.001] as in women [HR = 1.6 (0.9–2.7), P = 0.06 and HR = 1.8 (0.9–3.4), P = 0.09 for a 10-fold increase in hs-C-reactive protein]. The effect of log(Nt-proBNP) on CEP and CV death was significantly modulated by age (P < 0.001 and P = 0.01), but not by gender (P = 0.78 and P = 0.65), with significantly higher HRs in 71-year-old subjects [HR = 3.5 (2.4–5.2) and HR = 5.4 (3.4–8.4) for a 10-fold increase in Nt-proBNP, both H < 0.001] and 61-year-old subjects [HR = 2.9 (1.7–5.0) and HR = 4.2 (3.3–8.6) for a 10-fold increase in Nt-proBNP, both P < 0.001] compared to 41- or 51-year-old subjects [HR = 0.9 (0.5–1.6) and HR = 1.3 (0.5–3.8) for a 10-fold increase in Nt-proBNP, both P = 0.6]. The effect of log(UACR) on CEP and CV death was neither modulated by age (P = 0.11 and P = 0.86) nor gender (P = 0.45 and P = 0.89).

The level of Nt-proBNP and to some degree hs-C-reactive protein predicted whether a myocardial infarction was fatal or non-fatal: the risk of a myocardial infarction being fatal was 43% in subjects with high Nt-proBNP when compared with 3.7% in subjects with low Nt-proBNP, whereas hs-C-reactive protein only increased the risk from 14.3–35.1% and high UACR did not change the risk at all (29–30%).

In multivariable Cox-regression analysis without adjustment for other risk factors, CEP was independently predicted by log(hs-C-reactive protein)/SD [HR = 1.3 (1.2–1.5), log(UACR)/SD [HR = 1.5 (1.3–1.6)], and log(Nt-proBNP)/SD [HR = 1.7 (1.5–2.0), all P < 0.001]. Similarly, CV death was independently predicted by log(hs-C-reactive protein)/SD [HR = 1.3 (1.1–1.6), P = 0.002], log(UACR)/SD [HR = 1.5 (1.3–1.7)], and log(Nt-proBNP)/SD [HR = 2.1 (1.9–2.6), both P < 0.001]. CEP and CV death were also predicted by hs-C-reactive protein, UACR, and Nt-proBNP independently using dichotomy variables based on the median values without any significant interactions (Figure 1). For both endpoints, Nt-proBNP contributed the most and hs-C-reactive protein protein the least. In 399 subjects with

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics for women and men</th>
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<tr>
<td><strong>Median (IQR)</strong></td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>Waist/hip ratio (ratio)</td>
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<tr>
<td>Plasma glucose (mmol/L)</td>
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<td>Serum insulin (pmol/L)</td>
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<td>Systolic BP (mmHg)</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<td>Heart rate (min⁻¹)</td>
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<td>PWV (mmHg)</td>
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<td>LV mass index (g/m²)</td>
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<tr>
<td>LV EF (%)</td>
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<tr>
<td>UACR (mg/mmol)</td>
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<tr>
<td>hsCRP (mg/L)</td>
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<tr>
<td>NT-proBNP (pg/mL)</td>
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BP, blood pressure; RWT, relative wall thickness.
all three markers above the median values, the incidence of CEP was of 21.3% (85/399) and incidence of CV death was of 16.5% (66/399) as compared to 1.6% (6/365) and 0.8% (3/365) in subjects with all three markers below the median values (n = 365) resulting in HRs of 16.4(7.1–37.4) and 24.6(7.7–78.2), respectively (both P-values < 0.001).

Adjusted prognostic value of UACR, high sensitivity C-reactive protein, and Nt-proBNP

In Table 2, the standardized HRs for log(UACR)/SD, log(hs-C-reactive protein)/SD, and log(Nt-proBNP)/SD were progressively adjusted for established CV risk factors. All the established CV risk factors from Table 1 were included, but only the factors presented in Table 2 turned out to have independent impacts on CEP or CV death. All three novel CV risk markers remained significant after adjustment for traditional CV risk factors, but when including markers of subclinical CV damage (L VEF and relative wall thickness) only log(UACR)/SD and log(Nt-proBNP)/SD had significant impact on CEP and CV death (Table 2). Furthermore, they had additive effects with significant HRs after adjusting for each other (Table 2). Log(UACR)/SD and log(Nt-proBNP)/SD were the two strongest continuous predictors of CEP as well as CV death surpassing every one of the traditional CV risk factors. In Appendix 1, Log(UACR) and log(Nt-proBNP) and to less degree log(hs-C-reactive protein) added significantly to the Cox-regression model based on traditional CV risk factors, and log(Nt-proBNP) added also to the model with log(UACR). Using forced Cox models did not change the results significantly (data not shown).

Already at relatively low levels of log(UACR), log(hs-C-reactive protein), and log(Nt-proBNP), the calculated absolute risk of CEP and CV death increased and continued to increase gradually with increasing levels of the novel risk markers (Figure 2). Although the unadjusted curves indicated a cut-off value after which the risk increased dramatically, there were no cut-off value after adjusting for age, gender, CV disease, and diabetes (Figure 2).

CV risk functions

Based on the Cox-regression models using traditional CV risk factors with or without the novel CV risk markers, CV risk functions were created (Appendix 1) and used to construct ROC plots for predicting CEP or CV death in the population. The areas under all the ROC plots were not significantly different (Table 3). Excluding individuals with known diabetes, prior stroke or myocardial infarction (n = 188) did not change the results significantly, nor were the results affected by including L VEF and relative wall thickness (data not shown).

Discussion

This study has three novel findings: first, even relatively small increases in UACR, hs-C-reactive protein, and Nt-proBNP were associated with increasing CV risk. Secondly, they carried additive prognostic information. Thirdly, higher Nt-proBNP and higher UACR, but not higher hs-C-reactive protein predicted CV events after adjustment for established CV risk factors in the general population.

The association of UACR, high sensitivity C-reactive protein, and Nt-proBNP to CV risk

Although most of the subjects had normoalbuminuria (UACR < 3.5 mg/mmol), the CV risk clearly increased with increasing UACR within the so-called normal range supporting prior studies arguing for a lower threshold.6,18 In parallel CV risk also increased at levels of hs-C-reactive protein (<3.0 mg/L)4 and Nt-proBNP (<125 pg/mL)19 regarded as normal, supporting the concept that these novel risk markers are continuous variables associated with gradually-increasing CV risk and that levels regarded as normal in patients may be abnormal in the general population.

Additive prognostic value of UACR, high sensitivity C-reactive protein, and Nt-proBNP

Before adjustment for established CV risk factors, UACR, hs-C-reactive protein, and Nt-proBNP carried additive prognostic information supporting the concept that UACR, hs-C-reactive protein, and Nt-proBNP through their association with different CV risk factors are markers of damage in different parts of the CV system. High UACR reflects microvascular damage,20 high Nt-proBNP reflects CV damage and L V dysfunction,31 and hs-C-reactive protein
reflects atherosclerosis. Although high vs. low values of the three novel CV risk markers were almost equally associated with CV events, the continuous variables log(Nt-proBNP)/SD and log(UACR)/SD were superior to log(hs-C-reactive protein)/SD in predicting CEP and CV death, indicating that higher UACR and higher Nt-proBNP were associated with higher CV risk at all levels. As previous demonstrated, Nt-proBNP predicted CV death in particular and high vs. low Nt-proBNP were associated with an 10-fold higher risk of a subsequent myocardial infarction being fatal. In Figure 1B, subjects with low Nt-proBNP had low CV mortality despite hs-C-reactive protein and high UACR.

Prognostic value independently of other CV risk factors

All three new, emerging CV risk markers remained significant after adjustment for traditional CV risk factors, but only UACR and Nt-proBNP remained significant after adjustment for markers of subclinical CV damage suggesting that UACR and Nt-proBNP were markers of subclinical CV disease not fully detectable by echocardiography or PWV measurements. However, the predictive value of hs-C-reactive protein decreased gradually with further adjustment indicating that it was the sum of established CV risk factors rather than markers of subclinical CV damage which reduced the prognostic effect of hs-C-reactive protein to an insignificant level. This is in agreement with the findings by Danesh et al., who demonstrated that hs-C-reactive protein was a moderate predictor of coronary heart disease, and by Kistorp et al., who showed that hs-C-reactive protein was not as strongly associated to CV outcome as Nt-proBNP and UACR. Indeed, the predictive value of all three markers decreased almost equally during the cumulative adjustment for CV risk factors supporting that they all were related to CV risk factors. However, only UACR and Nt-proBNP carried additive prognostic information reflecting the fact that hs-C-reactive protein is closer related to CV risk factors than to CV damage suggesting that hs-C-reactive protein is a marker especially of the atherosclerotic process and thereby early atherosclerosis. Therefore, hs-C-reactive protein was less appropriate to predict outcome in the current study population in which most endpoints occurred among elderly subjects with more advanced atherosclerosis. The reduced importance of hs-C-reactive protein as predictor of CV events in elderly subjects has also been shown in other studies. Furthermore, it is important to recognize that log(UACR)/SD and log(Nt-proBNP)/SD were the two strongest continuous predictors of CEP as well as CV death surpassing lipids, BP, heart rate, pulse wave velocity, LV hypertrophy, or LVEF.

Clinical implications

Nt-proBNP and UACR, but not hs-C-reactive protein, added significantly to the Cox-regression models independently of whether subjects with diabetes or known CV disease (prior stroke or myocardial infarction). However, they did not increase the area under the ROC plots significantly and around 90% of the CV events occurred in the half of the subjects with a calculated risk above the median value of any of the risk functions. Therefore, the prognostic improvement using UACR and Nt-proBNP was only modest and further testing is needed in different subgroups and with different cut-off values in hope of better performance and possible clinical implication.
If identified, this high-risk subgroup could be a target for particularly aggressive risk factor intervention. Although this hypothesis has to be proven in future prospective intervention studies, it has been demonstrated that the plasma level hs-C-reactive protein is reduced by statin treatment and that levels of UACR as well as Nt-proBNP are reduced by antihypertensive treatment. However, at present only reduction in UACR has been demonstrated to translate into an improved prognosis independently of changes in traditional CV risk factors.

Limitations

As the data on prior CV disease was self-reported, we chose a conservative, but probably accurate definition using only prior myocardial infarction or prior stroke as prior CV disease. Although 30% of the originally examined subjects did not participate in this study, we think it is unlikely that this selection induced any bias because these subjects did not differ from the rest at the original examination. It was not possible to present gender-specific analyses due to lack of power in women, but only hs-C-reactive protein was modulated by gender in the Cox-regression analyses. We did not have data on serum creatinine. However, none of the subjects had known severe renal failure and excluding

**Table 3** Areas under the ROC plots predicting the composite endpoint and CV death based on different risk functions

<table>
<thead>
<tr>
<th>CV risk function</th>
<th>CEP</th>
<th>CV death</th>
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<tbody>
<tr>
<td>Traditional RF</td>
<td>0.82(0.79-0.85)</td>
<td>0.87(0.85-0.90)</td>
</tr>
<tr>
<td>Traditional RF and high sensitivity C-reactive protein</td>
<td>0.82(0.79-0.85)</td>
<td>0.87(0.84-0.90)</td>
</tr>
<tr>
<td>Traditional RF and UACR</td>
<td>0.83(0.80-0.86)</td>
<td>0.88(0.85-0.91)</td>
</tr>
<tr>
<td>Traditional RF and Nt-proBNP</td>
<td>0.83(0.81-0.86)</td>
<td>0.88(0.86-0.91)</td>
</tr>
<tr>
<td>Traditional RF, UACR and Nt-proBNP</td>
<td>0.84(0.81-0.86)</td>
<td>0.88(0.86-0.91)</td>
</tr>
</tbody>
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RF, cardiovascular risk factors.
subjects with UACR above 3.5 mg/mmol did not change the results significantly.

Conclusion

The CV risk increased already at relatively low levels of UACR, serum Nt-proBNP, and hs-C-reactive protein, and they carried additive prognostic information, but only serum Nt-proBNP and UACR predicted CEP and CV death after adjustment for established CV risk factors. However, as serum Nt-proBNP and UACR did not increase the area under the ROC plots significantly, more studies in relevant subgroups are needed before Nt-proBNP and UACR can be recommended for risk prediction and selection of subjects for primary prevention in the general population.

Acknowledgements

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Conflict of interest: none declared.

Appendix 1

Constants and coefficients generated from Cox-regression analyses used in the CV risk functions for the composite endpoint.

References


