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High-sensitive troponin T and N-terminal pro-B type natriuretic peptide are associated with cardiovascular events despite the cross-sectional association with albuminuria and glomerular filtration rate

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Aims It has been suggested that troponins and natriuretic peptides can be falsely elevated in subjects with impaired kidney function because of decreased renal clearance. The value of these biomarkers in subjects with impaired kidney function has therefore been debated. We tested in a population-based cohort study, first, whether high-sensitive troponin T (hsTnT) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels are cross-sectionally associated with the estimated glomerular filtration rate (eGFR) and albuminuria, and secondly, whether these markers are associated with cardiovascular outcome, independent of eGFR, albuminuria and conventional cardiovascular risk factors.

Methods and results We included 8121 subjects from the PREVEND study with both values of hsTnT and NT-pro-BNP available. High-sensitive troponin T >0.01 μg/L and NT-pro-BNP >125 ng/L were defined as elevated. We first performed linear regression analyses with hsTnT and NT-pro-BNP as dependent variables. Next, we performed Cox-regression analyses, studying the associations of hsTnT and NT-pro-BNP with incident cardiovascular events. Of our cohort, 6.7% had an elevated hsTnT and 12.2% an elevated NT-pro-BNP. Also, the estimated glomerular filtration rate, albuminuria, and ECG-assessed ischaemia and left ventricular hypertrophy were all significantly associated with hsTnT and NT-pro-BNP in the linear regression analyses. Both hsTnT and NT-pro-BNP appeared associated with cardiovascular events, and these associations remained significant after adjustment for eGFR, albuminuria, age, gender and conventional cardiovascular risk factors ($P = 0.03$ and $P < 0.001$, respectively). Only a few subjects with markedly reduced renal function were included. The results presented are therefore mainly valid for a population with mildly impaired renal function.

Conclusion These data indicate that a finding of an increased hsTnT or NT-pro-BNP in subjects with chronic kidney disease stages 1/3 should be taken seriously as a prognostic marker for a worse cardiovascular outcome and not be discarded as merely a reflection of decreased renal clearance.

Keywords Troponin • BNP (natriuretic peptide) • Albuminuria • eGFR • Cardiovascular outcome

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Introduction

Recently various biomarkers related to subclinical cardiovascular disease have drawn attention for clinical use in patients with cardiovascular symptoms and in epidemiological research to predict the cardiovascular prognosis. This applies among others to troponins and N-terminal pro-B-type natriuretic peptides (NT-pro-BNP).[1–3] It has therefore been suggested that these markers could be used in addition to 'conventional' cardiovascular risk factors to improve the cardiovascular risk estimation.[4,5]

Cardiac troponin T (TnT) is a sensitive and specific marker of ischaemic myocardial damage and is widely used as predictor of cardiovascular events.[1] Recently, a new, more sensitive troponin assay has been released, which can measure substantially lower concentrations than previous assays. High-sensitive troponin T (hsTnT) has been shown to be a powerful predictor of mortality.[6] Natriuretic peptides, including BNP and its equimolarly secreted N-terminal fragment (NT-pro-BNP), are increased in relation to cardiac stretch[7] and left ventricular hypertrophy, and are established biomarkers for guiding the diagnosis, prognosis and management in patients with established cardiovascular disease and heart failure.[4,8,9] Plasma NT-pro-BNP has been shown to independently predict the all-cause mortality and cardiovascular events.[3]

In subjects with decreased estimated glomerular filtration rate (eGFR) or increased albuminuria, the use of these cardiac biomarkers has been debated. It has been suggested that especially in subjects with impaired renal function BNP may be falsely elevated. Because of decreased renal clearance, BNP is thought to be increased, even when there are no overt signs of volume overload or left ventricular hypertrophy.[10–14] Similarly, it has been argued that TnT levels are elevated in patients with impaired renal function even when there is no evidence of coronary artery stenosis.[15,16] On the other hand, the predictive value of TnT and NT-pro-BNP for cardiovascular events has been shown to be maintained in such subjects.[8,17,18] The association of urinary albumin excretion (UAE) with hsTnT and NT-pro-BNP has yet not been studied.

We hypothesized that hsTnT and NT-pro-BNP are elevated in subjects with lower eGFR or higher albuminuria, not because of decreased renal clearance, but because these markers truly reflect subclinical cardiac damage. We therefore tested in a population-based cohort study, first, whether serum levels of hsTnT and NT-pro-BNP are associated with eGFR and albuminuria, and with minor ischaemic changes and/or left ventricular hypertrophy on electrocardiography (ECG). Secondly, we studied whether these cardiac biomarkers are associated with cardiovascular outcome, independent of the eGFR and albuminuria.

Methods

Study design and population

This study was conducted among subjects who participate in the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study, which started in 1997. This prospective cohort study investigates the natural course of albuminuria and its relation to renal and cardiovascular disease. Details of the study protocol have been published elsewhere.[19,20]

In summary, all inhabitants of the city of Groningen aged 28–75 years were sent a questionnaire on demographics, disease history, smoking habits, use of medication, and a vial to collect a first-morning-void urine sample. Of these subjects, 40 856 responded (47.8%). From these subjects, the PREVEND cohort was selected with the aim to create a cohort enriched for the presence of high albuminuria. After exclusion of patients with type 1 diabetes mellitus (defined as requiring the use of insulin) and pregnant females (defined by self-report), all subjects with a urinary albumin concentration >10 mg/L (7768) were invited, of which 6000 participated. Furthermore, a randomly selected control group with a urinary albumin concentration of <10 mg/L (3394) was invited, of which 2592 participated. These 8592 subjects constitute the actual PREVEND cohort and were studied in more detail.

For the current study, we excluded 471 subjects with no data on hsTnT or NT-pro-BNP at baseline, leaving 8121 subjects for analysis, which is also graphically shown in *Figure 1*. The PREVEND study was approved by the medical ethics committee of our institution and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

Measurements and definitions

At the baseline visit anthropometrical measurements were performed, and fasting blood samples were taken. In addition, subjects collected urine for two consecutive periods of 24 h. The blood pressure was measured in the supine position, every minute for 10 and 8 min, respectively, with an automatic device (Dinamap XL Model 9300; Johnson-Johnson Medical, Tampa, FL, USA). The blood pressure is given as the mean of the last two recordings of both visits.

Concentrations of the total cholesterol and the plasma glucose were measured using standard methods. Serum creatinine was measured by dry chemistry (Eastman Kodak, Rochester, New York, USA), with an intra-assay coefficient of variation of 0.9% and inter-assay coefficient of variation of 2.9%. The urinary albumin concentration was measured by nephelometry with a threshold of 2.3 mg/L and intra- and inter-assay coefficients of variation of 2.2 and 2.6%, respectively (BNII; Dade Behring Diagnostic, Marburg, Germany). The urinary albumin excretion is given as the mean of the two 24-h urine collections. High-sensitive troponin T (fifth generation cTnT assay) and NT-pro-BNP were all measured on the Roche Modular E170 (Roche Diagnostics, Mannheim, Germany) with commercially available kits.[3] An increased level of hsTnT was defined as a level >0.01 μg/L.[21] An increased level of NT-pro-BNP was defined when the level at baseline was >125 ng/L.[22–24]

Participants were considered as smoking when they had smoked in the previous year according to the questionnaire. Cardiovascular history was defined as self-reported myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or cerebrovascular accident. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication according to self-report or to pharmacy data following the JNC-7 criteria. Hyperlipidaemia was defined as a cholesterol level >6.0 mmol/L when a history of hyperlipidaemia was present, or a cholesterol level of >6.5 mmol/L when a history of hyperlipidaemia was absent, or the use of lipid-lowering drugs. Diabetes was defined as a fasting glucose level >7.0 mmol/L or non-fasting glucose level of >11.1 mmol/L or the use of anti-diabetic medication following the ADA criteria. The estimated glomerular filtration rate was estimated using the chronic kidney disease (CKD)-EPI equation.[25] The body mass index was calculated as the ratio of the weight and the square of the height (weight/height^2). Minor ischaemic changes on the ECG were defined using the Minnesota code classification system for electrocardiographic findings, codes 1, 4, and 5.[23] Left ventricular hypertrophy on the ECG was defined

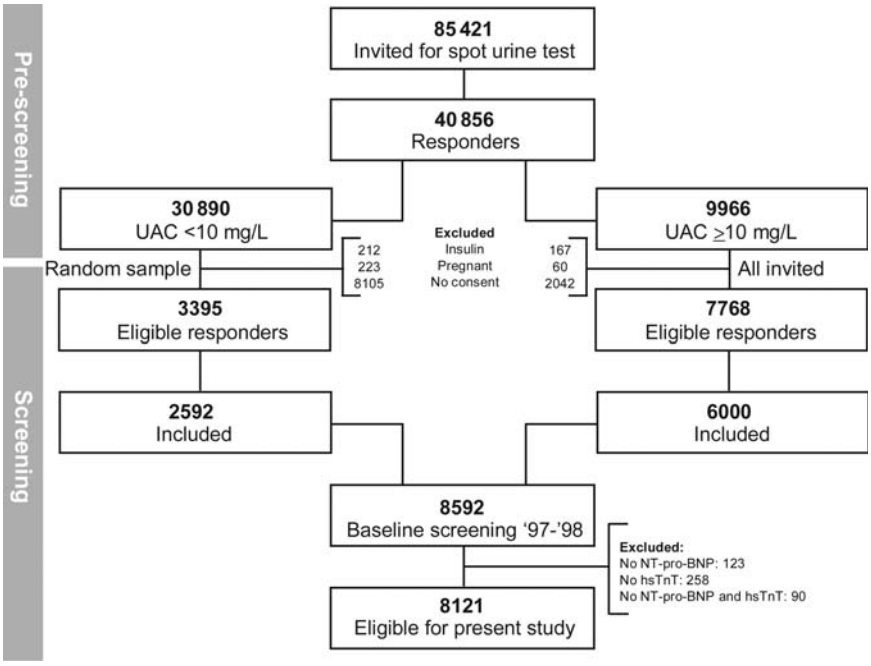

Figure 1 Flow chart of the PREVEND study.

using the Cornell criteria: RaVL + SV_3 (with 6 mm added in women) × the QRS duration. A threshold of 2440 mm*ms was used to identify left ventricular hypertrophy.[26,27]

Cardiovascular events

For the cardiovascular outcome, we used the incidence of the combined outcome of the cardiovascular morbidity and mortality. The date and cause of death were obtained by record linkage with the Dutch Central Bureau of Statistics. Information on hospitalization for cardiovascular morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. All data were coded according to the International Classification of Diseases, 9th revision and the classification of interventions. For this study, cardiovascular events were defined as incident acute myocardial infarction (ICD-code 410), acute and subacute ischaemic heart disease (411), and coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

Statistical analysis

All calculations were performed with the SPSS version 18.0 software. Continuous data are reported as mean ± SD. In the case of a skewed distribution, the median with the inter-quartile range is presented. Differences between groups for continuous data were tested by Student's *t*-test or a Mann–Whitney rank test in case of skewed distribution. Differences between groups for proportions were tested with a χ^2 test.

We first performed cross-sectional analyses with hsTnT and NT-pro-BNP as dependent variables in multivariable linear regression analyses. In these analyses, the eGFR and UAE were entered as independent variables (model 1), with subsequent adjustment for age and gender (model 2) and traditional cardiovascular risk factors (model 3), and finally with additional adjustment for ECG-assessed minor cardiac ischaemia and left ventricular hypertrophy (model 4). Because both cardiac variables, hsTnT and NT-pro-BNP, are not normally distributed, these variables were logarithmically transformed to meet the assumptions for linear regression analyses. The relation between hsTnT, respectively, NT-pro-BNP and the GFR and UAE was compatible with a linear relationship.

A KDIGO-initiated working group recently proposed that CKD should be defined on the basis of the level of the eGFR as well as on the level of albuminuria.[28] The prevalence of having a higher hsTnT and NT-pro-BNP was therefore studied with logistic regression analyses in relation to clinically relevant categories of the eGFR as well as UAE[29] and compared with the prevalence in a GFR × albuminuria reference category assumed to be at the lowest risk for cardiovascular events (eGFR 90–104 mL/min/1.73 m^2 and UAE <10 mg/24 h).[30–32] In case eGFR × albuminuria categories contained <20 subjects, no odds ratios (OR) were calculated because of insufficient power.

We next performed univariable and multivariable Cox-regression analyses to investigate the association of hsTnT or NT-pro-BNP with incident cardiovascular events, respectively. Univariable Cox-regression analyses were performed for hsTnT and NT-pro-BNP (model 1), respectively, with subsequent adjustment for the eGFR and UAE (model 2), age and gender (model 3), and finally with additional adjustment for traditional cardiovascular risk factors (model 4). Furthermore, hsTnT and NT-pro-BNP were simultaneously entered in the various models. In addition, it was investigated whether there was an interaction between hsTnT and NT-pro-BNP on the one hand and the eGFR on the other to check whether a possible relation between these cardiac damage biomarkers and cardiovascular events is indeed independent of renal function. This was done by adding the interaction term hsTnT (or NT-pro-BNP) × eGFR to the full adjusted model containing also both variables as single terms. For Cox-regression analyses, survival time was defined as the period from the date of urine collection of the participant to the date of the first cardiovascular event or 1 January 2009 (end of follow-up). Subjects were censored in case they died or moved to an unknown destination.

Since the PREVEND study is enriched for subjects with higher albuminuria levels, sensitivity analyses were performed using weighted analyses,

adjusting for the study design.[33] Furthermore, the aforementioned analyses were also performed only in subjects with chronic kidney disease (eGFR <60 mL/min/1.73 m^2 and/or albuminuria >30 mg/24 h).

For all analyses, a two-sided *P*-value <0.05 was considered to indicate statistical significance.

Results

For the present analyses, 8121 subjects were included of whom data on both hsTnT as well as NT-pro-BNP were available (*Figure 1*). Approximately 50% of the cohort consisted of male subjects, with a mean age of 49.3 ± 12.7 years (*Table 1*). Our study population comprised 1505 subjects (18.5% of the overall population) with CKD. Of these subjects 231 (2.8%) had CKD stage 1 (eGFR >90 mL/min/1.73 m^2 and UAE >30 mg/day), 800 (9.9%) stage 2 (eGFR 60–90 mL/min/1.73 m^2, and UAE >30 mg/day), 419 (5.2%) stage 3a (eGFR 45–60 mL/min/1.73 m^2), 46 (0.6%) stage 3b (eGFR 30–45 mL/min/1.73 m^2), and 9 (1.0%) stage 4 or 5 (eGFR 15–30 and <15 mL/min/1.73 m^2, respectively). More detailed information on the distribution over the various eGFR × albuminuria categories is given in Supplementary material online, *Tables S1* and *S2*. High-sensitive troponin T was >0.01 μg/L in 544 subjects (6.7%) and NT-pro-BNP was >125 ng/L in 984 subjects (12.1%). Subjects with a high hsTnT, as well as subjects with a high NT-pro-BNP, had a worse cardiovascular risk profile and had more ECG-assessed ischaemic changes and left ventricular hypertrophy. Subjects with high cardiac biomarkers had also more often a lower eGFR and higher albuminuria.

The association of high-sensitive troponin T and N-terminal pro-B-type natriuretic peptide with estimated glomerular filtration rate and albuminuria

The estimated glomerular filtration rate and UAE were associated with hsTnT (*P* < 0.001) (*Table 2*) and NT-pro-BNP (*P* < 0.001) (*Table 3*) (model 1), even after adjustment for age and gender (model 2) and further adjustment for cardiovascular risk factors (model 3) and the presence of ischaemic changes and left ventricular hypertrophy on ECG (model 4).

The OR of having an elevated hsTnT (>0.01 μg/L) or an elevated NT-pro-BNP (>125 ng/L) is given in *Figure 2*, for each eGFR × UAE category compared with the reference category of eGFR 90–104 mL/min/1.73 m^2 and UAE <10 mg/24 h (see also Supplementary material online, *Tables S1* and *S2*). These figures and tables show that the risk increased with a lower eGFR as well as with higher albuminuria. Of note, in not all eGFR× albuminuria categories an OR is given, because of a lack of power in these cells (subject number in a cell <20).

The association of high-sensitive troponin T and N-terminal pro-B-type natriuretic peptide with cardiovascular events

During follow-up 583 cardiovascular events (7.2%) were observed, which consisted of incident acute myocardial infarction (*n* = 243), acute and subacute ischaemic heart disease (*n* = 178), and coronary artery bypass grafting (*n* = 67) or percutaneous transluminal coronary angioplasty (*n* = 95). High-sensitive troponin T (*Table 4*) and NT-pro-BNP (*Table 5*) were associated with incident cardiovascular events, both univariably (model 1) as well as after adjustment for eGFR and albuminuria (model 2) and further adjustment for age and gender (model 3) and cardiovascular risk factors (model 4). Of note, the eGFR and UAE were not significantly associated with the cardiovascular outcome in this last multivariate model (model 4). *Figure 3* shows adjusted hazard ratios (HR) for cardiovascular events according to CKD status and low or high hsTnT or BNP. A higher level of NT-pro-BNP is associated with a higher risk of cardiovascular events, in non-CKD (adjusted HR: 1.49, *P*-value 0.006) as well as CKD patients (adjusted HR: 1.55, *P*-value 0.008). A higher level of hsTnT was similarly associated with higher risk in the unadjusted analyses in non-CKD (HR: 3.3; *P*-value < 0.001) as well as CKD (HR: 2.7; *P*-value <0.001), whereas in the adjusted analyses a higher level of hsTnT was only associated with a higher risk in subjects with CKD (adjusted HR: 1.53, *P*-value 0.008) (non-CKD, hsTnT adjusted HR: 0.92, *P*-value 0.65).

We analysed whether there was an interaction between hsTnT and NT-pro-BNP on the one hand and eGFR on the other in their association with cardiovascular events in the full adjusted model (model 4). No such interactions were found (*P* = 0.78 and *P* = 0.38, respectively).

Sensitivity analyses

Several sensitivity analyses were performed. First, even though both hsTnT and NT-pro-BNP were entered simultaneously to the various Cox-regression models, only NT-pro-BNP remained significantly associated with cardiovascular events (Supplementary material online, *Table S3*). Secondly, the aforementioned analyses were repeated in subjects with chronic kidney disease only (eGFR <60 mL/min/1.73 m^2 and/or UAE >30 mg/24 h). Cox-regression analyses in these patients showed that hsTnT and NT-pro-BNP were still associated with cardiovascular events in crude as well as adjusted models (models 2–4) (Supplementary material online, *Tables S4* and *S5*). Thirdly, when all analyses were repeated using weighted models, adjusting for the study design, essentially similar results were obtained.

Discussion

We found that in this general population-based study both hsTnT and NT-pro-BNP are inversely associated with the eGFR and positively associated with albuminuria. We, moreover, showed that both cardiac damage biomarkers are still associated with cardiovascular events after adjustment for eGFR, albuminuria, and cardiovascular risk factors.

Our data of an increased hsTnT and NT-pro-BNP level in case of a lower eGFR is in agreement with the literature.[18,34] To our knowledge, the association of hsTnT and NT-pro-BNP level with albuminuria has yet not been studied specifically. The observation that the associations of these cardiac biomarkers with high albuminuria is comparable with the association of these biomarkers with a low eGFR may help shed new light on the assumption that cardiac biomarkers such as NT-pro-BNP are elevated in

Table 1 Baseline characteristics of the overall population and according to high-sensitive troponin T and N-terminal pro-B-type natriuretic peptide status

Variable	Total population (n = 8121)	HsTnT <0.01 μg/L (n = 7577)	>0.01 μg/L (n = 544)	P-value	NT-pro-BNP <125 ng/L (n = 7137)	>125 ng/L (n = 984)	P-value
Age (years)	49.3 ± 12.7	48.2 ± 12.2	64.2 ± 9.8	<0.001	47.9 ± 12.0	59.4 ± 12.6	<0.001
Male (%)	49.8	47.7	78.9	<0.001	51.0	42.0	<0.001
BMI (kg/m^2)	26.1 ± 4.2	26.0 ± 4.2	27.7 ± 4.0	<0.001	26.0 ± 4.2	26.6 ± 4.5	<0.001
Smoking (%)	37.8	38.5	27.6	<0.001	38.2	35.1	0.066
CVD history (%)	5.2	4.2	19.5	<0.001	3.1	20.9	<0.001
SBP (mmHg)	129.1 ± 20.3	127.6 ± 19.2	148.6 ± 23.5	<0.001	127.3 ± 18.6	141.5 ± 26.7	<0.001
DBP (mmHg)	74.0 ± 9.8	73.5 ± 9.5	80.7 ± 10.6	<0.001	73.6 ± 9.5	77.0 ± 11.2	<0.001
Antihypertensive medication (%)	16.7	14.4	44.7	<0.001	12.7	42.7	<0.001
Hypertension (%)	33.4	30.3	77.0	<0.001	29.0	66.0	<0.001
Glucose (mmol/L)	4.9 ± 1.2	4.8 ± 1.1	5.5 ± 1.9	<0.001	4.9 ± 1.1	5.1 ± 1.4	<0.001
Glucose lowering medication (%)	1.6	1.2	6.8	<0.001	1.3	3.4	<0.001
Diabetes (%)	3.6	2.9	12.7	<0.001	3.1	7.2	<0.001
Cholesterol (mmol/L)	5.6 ± 1.1	5.6 ± 1.1	5.9 ± 1.1	<0.001	5.6 ± 1.1	5.7 ± 1.1	0.149
Lipid lowering medication (%)	4.1	3.7	9.8	0.173	3.2	10.2	0.022
Hyperlipidaemia (%)	26.6	25.6	40.1	<0.001	25.3	36.7	<0.001
Serum creatinine (μmol/L)	83.9 ± 19.7	82.6 ± 13.7	99.2 ± 26.0	<0.001	83.1 ± 13.7	89.7 ± 42.5	<0.001
Serum hsTnT (μg/L)	0.003 (0.003–0.005)	0.003 (0.003–0.004)	0.01 (0.01–0.02)	<0.001	0.003 (0.003–0.004)	0.005 (0.003–0.01)	<0.001
Serum NT-pro-BNP (ng/L)	37.7 (16.8–73.8)	35.5 (15.9–68.3)	105.9 (42.2–285.7)	<0.001	31.7 (14.8–56.7)	195.5 (150.1–327.7)	<0.001
Minor ischaemic changes (%)	23.2	21.5	48.8	<0.001	20.1	45.8	<0.001
LVH according to Cornell (%)	2.3	1.8	10.2	<0.001	1.6	7.2	<0.001
eGFR (mL/min/1.73 m^2)	83.9 ± 15.5	85.0 ± 14.8	68.9 ± 16.7	<0.001	85.3 ± 14.7	73.8 ± 17.4	<0.001
eGFR<60 (mL/min/1.73 m^2) (%)	5.9	4.4	27.9	<0.001	4.1	19.2	<0.001
UAE (mg/24 h)	9.4 (6.3–17.8)	9.1 (6.2–16.3)	23.1 (10.4–63.8)	<0.001	9.1 (6.3–16.1)	14.5 (7.3–41.0)	<0.001
UAE >30 (mg/24 h)	14.8	12.7	42.8	<0.001	12.6	30.7	<0.001

BMI, body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion

Table 2 Association between high-sensitive troponin T (log-transformed) as a dependent variable and estimated glomerular filtration rate and urinary albumin excretion as independent variables (model 1), and additionally age and gender (model 2), cardiovascular risk factors (model 3) and ECG abnormalities (model 4)

Variable	Model 1		Model 2		Model 3		Model 4	
	St B	*P*-value	St B	*P*-value	St B	*P*-value	St B	*P*-value
eGFR (mL/min/1.73 m^2)	−0.31	<0.001	−0.16	<0.001	−0.16	<0.001	−0.16	<0.001
Ln UAE (mg/24 h)	0.24	<0.001	0.14	<0.001	0.10	<0.001	0.09	<0.001
Age (years)			0.33	<0.001	0.29	<0.001	0.28	<0.001
Female (yes vs. no)			−0.26	<0.001	−0.24	<0.001	−0.24	<0.001
Smoking (yes vs. no)					0.02	0.02	0.02	0.02
Diabetes (yes vs. no)					0.06	<0.001	0.06	<0.001
CVD history (yes vs. no)					0.06	<0.001	0.05	<0.001
BMI (kg/m^2)					−0.004	0.66	0.01	0.49
SBP (mmHg)					0.12	<0.001	0.10	<0.001
Cholesterol (mmol/L)					−0.06	<0.001	−0.05	<0.001
Minor ischaemic ECG changes (yes vs. no)							0.06	<0.001
LVH according to Cornell (yes vs. no)							0.05	<0.001

UAE, urinary albumin excretion; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure.

Table 3 Association between N-terminal pro-B-type natriuretic peptide (log-transformed) as dependent variable and estimated glomerular filtration rate and urinary albumin excretion as independent variables (model 1), and additionally age and gender (model 2), cardiovascular risk factors (model 3) and ECG abnormalities (model 4)

Variable	Model 1		Model 2		Model 3		Model 4	
	St B	*P*-value	St B	*P*-value	St B	*P*-value	St B	*P*-value
eGFR (mL/min/1.73 m^2)	−0.29	<0.001	−0.07	<0.001	−0.06	<0.001	−0.06	<0.001
Ln UAE (mg/24 h)	0.10	<0.001	0.11	<0.001	0.09	<0.001	0.09	<0.001
Age (years)			0.33	<0.001	0.35	<0.001	0.33	<0.001
Female (yes vs. no)			0.32	<0.001	0.36	<0.001	0.36	<0.001
Smoking (yes vs. no)					0.02	0.12	0.01	0.13
Diabetes (yes vs. no)					−0.04	<0.001	−0.04	<0.001
CVD history (yes vs. no)					0.19	<0.001	0.16	<0.001
BMI (kg/m^2)					−0.13	<0.001	−0.11	<0.001
SBP (mmHg)					0.12	<0.001	0.09	<0.001
Cholesterol (mmol/L)					−0.16	<0.001	−0.16	<0.001
Minor ischaemic ECG changes (yes vs. no)							0.10	<0.001
LVH according to Cornell (yes vs. no)							0.07	<0.001

UAE, urinary albumin excretion; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; LVH, left ventricular hypertrophy (using Cornell criteria).

CKD predominantly because of impaired renal clearance.[13] If that would be the explanation, hsTnT and NT-pro-BNP levels would not be expected to be increased in case of higher albuminuria independent of the level of eGFR.

Our finding that these cardiac biomarkers are associated with cardiovascular events, as well as that this association persisted after adjusting for the level of the eGFR and albuminuria, is also in agreement with data from other studies.[8,17] The HR remained statistically significant after further adjusting for cardiovascular risk factors, indicating that these cardiac biomarkers can be used in subjects with impaired renal function to predict their cardiovascular prognosis.

As the prevalence of ECG-assessed minor ischaemic changes and left ventricular hypertrophy was higher in the high hsTnT and high NT-pro-BNP groups, we argue that the biomarkers are increased in subjects with a lower eGFR (and higher albuminuria), as they correctly reflect cardiac ischaemia and/or hypertrophy. It has indeed been reported that the cardiovascular abnormalities in subjects with impaired kidney function are due to more than just coronary heart disease.[35] Experimental models have shown that even a modest resection of renal parenchyma causes left ventricular hypertrophy, cardiac fibrosis, and microvessel disease with wall thickening of intramyocardial arterioles in the hypertrophied heart.[36]

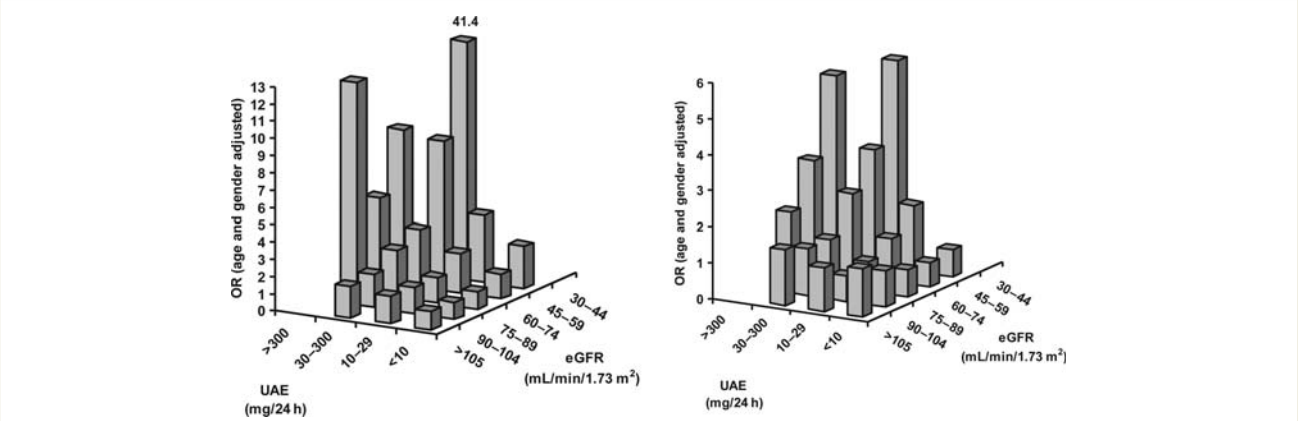

Figure 2 Odds ratios for increased high-sensitive troponin T (>0.01 μg/L) (left panel) and increased N-terminal pro-B-type natriuretic peptide (>125 ng/L) (right panel) per estimated glomerular filtration rate/albuminuria (urinary albumin excretion) class adjusted for age and gender, reference category being estimated glomerular filtration rate 90–104 mL/min/1.73 m^2 and UAE <10 mg/24 h.

Table 4 Hazard ratios for cardiovascular events with high-sensitive troponin T as an independent variable in various models adjusting for covariates

Variable	Model 1		Model 2		Model 3		Model 4	
	HR	*P*-value	HR	*P*-value	HR	*P*-value	HR	*P*-value
Ln hsTnT (μg/L)	2.15	<0.001	1.86	<0.001	1.25	0.002	1.18	0.03
eGFR (mL/min/1.73 m^2)			0.98	<0.001	0.99	0.21	0.99	0.08
Ln UAE (mg/24 h)			1.25	<0.001	1.17	<0.001	1.05	0.19
Age (years)					1.06	<0.001	1.05	<0.001
Female (yes vs. no)					0.47	<0.001	0.47	<0.001
Smoking (yes vs. no)							1.76	<0.001
Diabetes (yes vs. no)							1.22	0.17
CVD history (yes vs. no)							3.03	<0.001
BMI (kg/m^2)							1.04	0.001
SBP (mmHg)							1.01	<0.001
Cholesterol (mmol/L)							1.27	<0.001

HR, hazard rate; UAE, urinary albumin excretion; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure.

A higher hsTnT and NT-pro-BNP in relation to both a lower eGFR and higher albuminuria are, moreover, in line with recent data that the eGFR and albuminuria independently of each other predict cardiovascular mortality in subjects of the general population,[29] in subjects selected for an increased cardiovascular risk[30] and in subjects with known CKD.[31] The aforementioned observations taken together indicate that a finding of an increased hsTnT or NT-pro-BNP in a subject with a lower eGFR should be taken seriously as a prognostic marker for a worse cardiovascular outcome and not be discarded as merely the result of decreased renal clearance.

The similarity of the association of hsTnT levels with both ECG-assessed minor ischaemia as well left ventricular hypertrophy in our study is striking. Although TnT elevation is assumed to be the result of clinically silent myocardial necrosis and micro-infarctions[37] TnT has also been found to be elevated in patients with heart failure in the absence of acute ischaemia [38,39] and in CKD patients with left ventricular hypertrophy without myocardial ischaemia.[40] Our study also showed that NT-pro-BNP was not only associated with left ventricular hypertrophy, but also with ECG-assessed minor ischaemia. Experimental models have shown that hypoxic myocardial tissue results in the production of extra BNP, suggesting that BNP could potentially serve as a biomarker of myocardial ischaemia.[41,42] These experimental data were confirmed in a number of small-scale clinical studies, which were recently summarized in a meta-analysis.[43] These data indicate that BNP is not only linked to left ventricular hypertrophy and heart failure, but that there is a possible role for BNP also in the diagnosis and management of myocardial ischaemia.

Our findings that the associations of the GFR and albuminuria with cardiovascular events lose significance in the overall multivariable adjusted model although both hsTnT and NT-pro-BNP remained significantly associated with cardiovascular event suggest that both hsTnT and NT-pro-BNP may help to detect

Table 5 Hazard ratios for cardiovascular events with N-terminal pro-B-type natriuretic peptide as an independent variable in various models adjusting for covariates

Variable	Model 1		Model 2		Model 3		Model 4	
	HR	*P*-value	HR	*P*-value	HR	*P*-value	HR	*P*-value
Ln NT-pro-BNP (ng/L)	1.57	<0.001	1.31	<0.001	1.22	<0.001	1.17	<0.001
eGFR (mL/min/1.73 m^2)			0.98	<0.001	0.99	0.18	0.99	0.06
Ln UAE (mg/24 h)			1.30	<0.001	1.16	<0.001	1.04	0.32
Age (year)					1.06	<0.001	1.04	<0.001
Female (yes vs. no)					0.40	<0.001	0.41	<0.001
Smoking (yes vs. no)							1.76	<0.001
Diabetes (yes vs. no)							1.31	0.07
CVD history (yes vs. no)							2.68	<0.001
BMI (kg/m^2)							1.04	<0.001
SBP (mmHg)							1.01	<0.001
Cholesterol (mmol/L)							1.29	<0.001

UAE, urinary albumin excretion; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure.

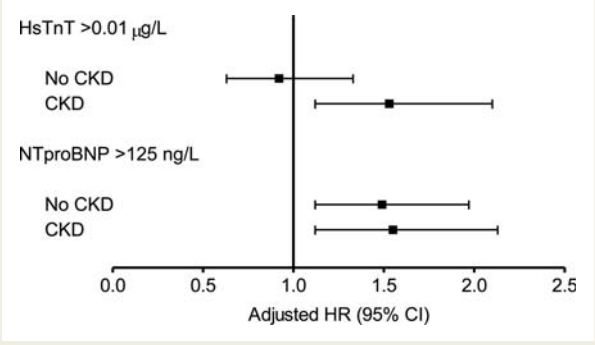

Figure 3 Adjusted hazard ratios for cardiovascular events according to CKD status and low- or high-sensitive troponin T or N-terminal pro-B-type natriuretic peptide. Hazard ratios are calculated with subjects with corresponding CKD status and normal high-sensitive troponin T or N-terminal pro-B-type natriuretic peptide (<0.01 µg/L or <125 ng/L, respectively) as reference groups. Adjusted hazard ratios are adjusted for age, gender, history of cardiovascular disease, smoking, BMI, SBP, cholesterol level and diabetes.

subjects with impaired kidney function and/or higher albuminuria at risk for cardiovascular events. These data, moreover, encourage further research on the mechanism of how mild CKD is associated with a worse cardiovascular outcome.

Strengths of this study are the use of a large prospective community-based cohort with detailed information on many covariates. A limitation of the PREVEND cohort is that it includes a predominantly Caucasian population and a relatively small number of subjects with CKD stages 4 and higher (eGFR <30 mL/min/1.73 m^2). Our findings can therefore not be generalized to other populations, nor to subjects with severely impaired kidney function. Furthermore, the PREVEND cohort is by design enriched with subjects with higher albuminuria. Since sensitivity analyses adjusting for the study design showed similar results, this is not expected to have resulted in a bias.

In conclusion, hsTnT and NT-pro-BNP are increased in subjects with a lower eGFR and/or higher albuminuria. Both cardiac damage biomarkers are associated with ECG-assessed minor ischaemia and left ventricular hypertrophy independent of eGFR and albuminuria. In subjects with their impaired kidney function and/or albuminuria, TnT and NT-pro-BNP are associated with cardiovascular outcome independent of the level of the eGFR and albuminuria. These effects are independent of cardiovascular risk factors. The present study included only a limited number of subjects with markedly reduced renal function. Notwithstanding, our data indicate that increased levels of these cardiac biomarkers in subjects with CKD stages 1/3 should be considered seriously and not be discarded as merely the result of decreased renal clearance. These data may furthermore help to dissect the mechanism by which even mild chronic kidney disease results in cardiac damage.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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Single heterozygote splice mutation in the *ABCA1* gene is associated with diffuse atherosclerotic disease in a low high-density lipoprotein syndrome

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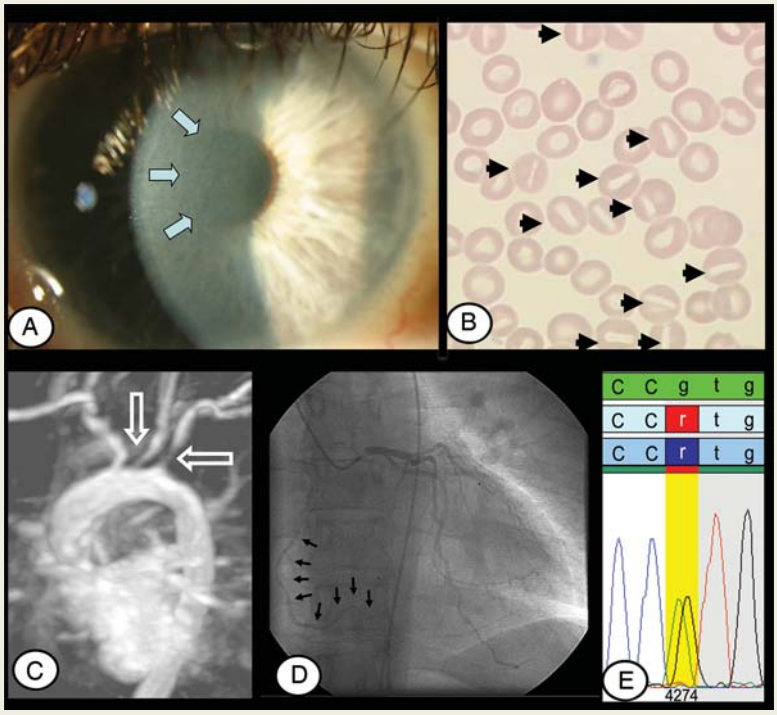

A 50-year-old woman was referred with a 6-month history of dyspnoea. She presented with obesity (body mass index: 40.9 kg/m^2), blood pressures of 140/80 mmHg on the right arm and 100/70 mmHg on the left, a left subclavian bruit, and corneal clouding covering the pupil (*Panel A*). Laboratory tests were notable for haemoglobin of 9.9 g/dL (normal: 12–16), stomatocytes (*Panel B*) and a platelet count of 78 000/mL (normal: 150 000–400 000). C-reactive protein was normal. The total cholesterol was 189 mg/dL (normal: <200 mg/dL), triglycerides were 265 mg/dL (normal: <150), HDL was 3 mg/dL (normal: >35), and apolipoprotein-A1 was 11 mg/dL (normal: 105–205). Doppler-ultrasound and magnetic resonance angiography demonstrated moderate stenoses of the proximal left internal carotid and subclavian arteries (*Panel C*). Echocardiography showed normal pulmonary artery pressures and left ventricular function. Coronary angiography indicated mild left main stenosis and a collateralized total occlusion of the right coronary artery (*Panel D*); no inducible ischaemia was appreciated by dobutamine stress testing.

Based on the low HDL, diffuse atherosclerosis, and the stomatocytosis, we suspected an impairment of the ATP-binding cassette transporter 1 protein. ABCA1 responsible for the cellular cholesterol and phospholipid efflux and may lead to vascular foam cell accumulation. Genetic analysis (electropherogram) identified an undescribed single heterozygote splice mutation of G > A (*Panel E*: 'r'; www.hgvs.org) at position 4274 of the cDNA (*ABCA1* gene) targeting the donor splice site of the intron 30.

With no objective evidence of ischaemia to explain her dyspnoea and without neurological symptoms or exertional arm discomfort, we elected to manage her vascular lesions medically. We targeted non-HDL goals with statin therapy and encouraged our patient to lose weight and avoid drugs that may lower the HDL cholesterol. We arranged a familial genetic counselling and will follow her up carefully.

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