# Estimated Glomerular Filtration Rate and Albuminuria Are Associated with Biomarkers of Cardiac Injury in a Population-Based Cohort Study

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# Estimated Glomerular Filtration Rate and Albuminuria Are Associated with Biomarkers of Cardiac Injury in a Population-Based Cohort Study: The Maastricht Study

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**BACKGROUND:** Chronic kidney disease (CKD) is associated with an increased cardiovascular disease mortality risk. It is, however, less clear at what point in the course from normal kidney function to CKD the association with cardiovascular disease appears. Studying the associations of estimated glomerular filtration rate (eGFR) and albuminuria with biomarkers of (subclinical) cardiac injury in a population without substantial CKD may clarify this issue.

**METHODS:** We examined the cross-sectional associations of eGFR and urinary albumin excretion (UAE) with high-sensitivity cardiac troponin (hs-cTn) T, hs-cTnI, and N-terminal probrain natriuretic-peptide (NT-proBNP) in 3103 individuals from a population-based diabetes-enriched cohort study.

**RESULTS:** After adjustment for potential confounders, eGFR and UAE were associated with these biomarkers of cardiac injury, even at levels that do not fulfill the CKD criteria. For example, eGFR 60–<90 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ [vs ≥90 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$] was associated with a [ratio (95% CI)] 1.21 (1.17–1.26), 1.14 (1.07–1.20), and 1.19 (1.12–1.27) times higher hs-cTnT, hs-cTnI, and NT-proBNP, respectively. The association of eGFR with hs-cTnT was statistically significantly stronger than that with hs-cTnI. In addition, UAE 15–<30 mg/24 h (vs <15 mg/24 h) was associated with a 1.04 (0.98–1.10), 1.08 (1.00–1.18), and 1.07 (0.96–1.18) times higher hs-cTnT, hs-cTnI, and NT-proBNP, respectively.

**CONCLUSIONS:** eGFR and albuminuria were already associated with biomarkers of (subclinical) cardiac injury at levels that do not fulfill the CKD criteria. Although reduced renal elimination may partly underlie the associations of eGFR, these findings support the concept that eGFR and albuminuria are, over their entire range, associated with cardiac injury.



Chronic kidney disease (CKD),[11] which is defined as an estimated glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ and/or a urinary albumin excretion (UAE) ≥30 mg/24 h, is associated with an increased cardiovascular disease (CVD) mortality risk *(1)*. It is, however, not entirely clear at what point in the course from normal kidney function to CKD the association with CVD risk appears *(1, 2)*. For example, GFR estimates that include cystatin C have been associated with CVD mortality at levels far above the 60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ threshold, whereas this is less clear for eGFR based on creatinine only *(2)*. In addition,

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[11] Nonstandard abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; CVD, cardiovascular disease; cTn, cardiac troponin; NT-proBNP, N-terminal probrain natriuretic-peptide; hs, high-sensitivity; hs-cTnT, high-sensitivity cardiac troponin T; hs-cTnI, high-sensitivity cardiac troponin I; T2DM, type 2 diabetes mellitus; $eGFR_{crcys}$, eGFR based on creatinine and cystatin C; $eGFR_{cr}$, eGFR based on creatinine; $eGFR_{cys}$, eGFR based on cystatin C; LoB, limit of blank; LoD, limit of detection; CV, coefficient of variation; Hb $A_{1c}$, hemoglogin $A_{1c}$; ECG, electrocardiogram; IQR, interquartile range; VEGF, vascular endothelial growth factor; NO, nitric oxide.

it is important to gain insight into the mechanisms that underlie the CVD mortality risk associated with eGFR and albuminuria. Studying the associations of eGFR levels ≥60 mL · $min^{-1}$ · $(1.73\ m^2)^{-1}$ and UAE levels <30 mg/24 h with biomarkers of (subclinical) cardiac injury, such as the cardiac troponins (cTn) T and I, and N-terminal probrain natriuretic-peptide (NT-proBNP) *(3, 4)*, may help in clarifying these issues. The interpretation of these biomarkers in the face of kidney disease is, nevertheless, controversial *(5)*.

In this regard, it is important to distinguish eGFR from albuminuria as both entities may be associated with biomarkers of cardiac injury via different mechanisms. For instance, reduced eGFR may cause cardiac injury via chronic low-grade inflammation and endothelial dysfunction *(6)*, but may also reduce the renal elimination of cTn and NT-proBNP *(5, 7)*. In contrast, albuminuria has been hypothesized to be a biomarker of generalized endothelial dysfunction *(8)* and capillary rarefaction *(9)*, which in turn may cause (subclinical) cardiac ischemia *(10)*, resulting in higher cTn and NT-proBNP concentrations *(3, 4)*. Indeed, the limited available data *(5, 11–13)* suggest that eGFR and albuminuria are mutually independently associated with cTn *(5, 11, 13)* and NT-proBNP *(11)*. However, only 2 of these studies have examined a population without substantial CKD *(11, 13)*.

In addition, only 2 studies have examined whether cTnT and cTnI behave similarly with regard to their associations with eGFR at levels ≥60 mL · $min^{-1}$ · $(1.73\ m^2)^{-1}$ *(14)* and with albuminuria *(5)*. This may be important as both cTn are used interchangeably in clinical practice, whereas cTnT has been suggested to be more strongly dependent on renal elimination than cTnI *(15)*. The latter is supported by stronger associations of eGFR *(5, 15–18)* and measured GFR *(19)* with cTnT than with cTnI at levels <60 mL · $min^{-1}$ · $(1.73\ m^2)^{-1}$, even when both cTn were measured with high-sensitivity (hs) assays *(5, 15, 17, 19)*.

In view of the above, we examined whether eGFR and albuminuria were, independently of each other, associated with hs-cTnT, hs-cTnI, and NT-proBNP in a population-based cohort, and whether these associations appeared at levels of eGFR and albuminuria, which do not fulfill the CKD criteria. In addition, we compared the strength of any associations of eGFR and albuminuria with hs-cTnT and hs-cTnI.

## Materials and Methods

### THE MAASTRICHT STUDY POPULATION AND DESIGN

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously *(20)*. In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus (T2DM) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November, 2010 and September, 2013. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088–105234-PG). All participants gave written informed consent. For this study, participants with type 1 diabetes or other specific types of diabetes (n = 41) were excluded. After further successively excluding participants whose eGFR based on creatinine and cystatin ($eGFR_{crcys}$) was missing (n = 33), whose 24-h urine collections were collected erroneously (<20 h or >28 h) or were not handed in at all (n = 42), and who had missing data on other variables in our primary regression models (n = 232), 3103 participants were included.

### KIDNEY FUNCTION

GFR was estimated with the CKD-EPI equation based on the combination of serum creatinine and serum cystatin C ($eGFR_{crcys}$) for the primary analyses (see Supplemental Methods that accompany the online version of this article at http://www.clinchem.org/content/vol63/issue4) *(21)*. For additional analyses, eGFR was calculated with the CKD-EPI equations based on serum creatinine ($eGFR_{cr}$) *(21)* and serum cystatin C ($eGFR_{cys}$) *(21)*.

To assess UAE, participants were requested to collect two 24-h urine collections (see the online Supplemental Methods). UAE was preferably based on the average of 2 (available in 91.9% of the participants) 24-h urine collections.

### CARDIAC BIOMARKERS

Fasting blood samples were collected from all participants and processed according to the manufacturers' instructions. Serum samples were stored at −80 °C for 1–4 years. hs-cTnT was measured on a Roche Cobas 6000 analyzer (Roche) with the Elecsys Troponin T hs assay (Roche), which has a limit of blank (LoB) of 3 ng/L, a limit of detection (LoD) of 5 ng/L, and achieves a 10% coefficient of variation (10% CV) at 13 ng/L. hs-cTnI

was measured on an Architect i2000 SR analyzer (Abbott Diagnostics) with the Architect STAT High Sensitive Troponin-I assay (Abbott), which has an LoB range of 0.7–1.3 ng/L, an LoD range of 1.1–1.9 ng/L, and achieves a 10% CV at 4.7 ng/L. NT-proBNP was assessed on a Roche Cobas 6000 analyzer (Roche) with the Elecsys proBNP II assay (Roche), which has a LoD of 5.0 ng/L (LoB not reported), and achieves a 20% CV at 50.0 ng/L.

#### COVARIATES

We collected data on glucose metabolism status, hemoglobin $A_{1c}$ (Hb $A_{1c}$), total cholesterol, HDL, LDL, triglycerides, waist circumference, office blood pressure, 24-h average ambulatory blood pressure, medication use, smoking behavior, alcohol consumption, educational level, questionnaire based prevalent CVD, resting 12-lead electrocardiogram (ECG), and self-reported physical activity as described previously *(20, 22)*. Please see the online Supplemental Methods for further details and definitions.

#### STATISTICAL ANALYSES

All analyses were performed with SPSS Statistics version 22.0 (IBM). Characteristics of the entire study population, and as categorized according to $eGFR_{crcys}$ and albuminuria, were summarized as means with SD, medians with interquartile ranges (IQRs), and numbers with percentages, as appropriate. The cardiac biomarkers are described with both actual mean (with SD) and median (with IQR) levels. However, given their positively skewed distributions, the median and IQR most accurately capture their central tendency and variation. For the comparison of participants across $eGFR_{crcys}$ and albuminuria categories, continuous variables were analyzed with one-way ANOVA if normally distributed and with the Kruskal–Wallis test if not. Categorical variables were compared with the $\chi^2$ test.

Associations of $eGFR_{crcys}$ and albuminuria with hs-cTnT, hs-cTnI, and NT-proBNP were evaluated with multivariable linear regression analyses. $eGFR_{crcys}$ and albuminuria were analyzed as categorical ($\geq$90, 60–$<$90, and $<$60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$; $<$15, 15–$<$30, and $\geq$30 mg/24 h) and as continuous (per $-$10 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$; per doubling of UAE) variables. To obtain similar proportions of individuals with a value above the LoB for hs-cTnT and hs-cTnI (87.1%, and 87.9%, respectively), the LoB of hs-cTnI was considered to be 0.9 ng/L. For both hs-cTnT and hs-cTnI, concentrations below the LoB were subsequently set at LoB/2. NT-proBNP concentrations below the LoD were set at LoD/2. Thereafter, concentrations of hs-cTnT, hs-cTnI, and NT-proBNP were natural logarithmically transformed. The regression coefficients were exponentiated to obtain the ratio of (geometric mean) concentrations of the cardiac biomarkers per 1 unit increase in the independent variable. We adjusted for potential confounders as follows: model 1, unadjusted model; model 2, age, sex, glucose metabolism status; model 3, model 2 + waist circumference, total-to-HDL cholesterol ratio, triglycerides, use of lipid-modifying medication, smoking behavior, alcohol consumption, educational level, $eGFR_{crcys}$/albuminuria; model 4a, model 3 + office systolic pressure, use of antihypertensive medication, ischemic ECG abnormalities; model 4b, similar to model 4a but adjusted for 24 h average ambulatory systolic pressure instead of office systolic pressure. Systolic pressure, use of antihypertensive medication, and ischemic ECG abnormalities were entered in a separate model as these may be both confounders and intermediates in the associations examined.

The distributions of hs-cTnT and hs-cTnI should be taken into account when comparing their associations with $eGFR_{crcys}$ and albuminuria. Therefore, we subsequently calculated partial correlations of $eGFR_{crcys}$ and albuminuria with hs-cTnT and hs-cTnI in model 4a and compared these with a test for comparing correlations measured on the same individuals *(23)*.

Several additional analyses were performed. First, analyses were repeated: in participants with UAE $\leq$300 mg/24 h and in participants with 2 valid urine collections; with additional adjustment for total and moderate to vigorous physical activity; and with alternative operationalizations of prior CVD, blood pressure, and the use of antihypertensive medication. Second, $eGFR_{crcys}$ was replaced with either $eGFR_{cr}$ or $eGFR_{cys}$. Third, we added interaction terms to model 4a to explore interaction with glucose metabolism status because glucose metabolism status has been shown to modify associations of other CVD risk factors with CVD events *(24)* ($P_{interaction}$ $<$0.10 was considered statistically significant). Fourth, to explore whether any association of $eGFR_{crcys}$ and albuminuria with (subclinical) cardiac injury could also be detected with an ECG, we examined their associations with ischemic ECG abnormalities.

## Results

#### CHARACTERISTICS OF THE STUDY POPULATION

Table 1 and online Supplemental Table 1 show the characteristics of the study population stratified according to $eGFR_{crcys}$ and albuminuria categories, respectively. Due to oversampling, 27.7% had T2DM. Average $eGFR_{crcys}$ was 88.2 (14.8) mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$. Most participants had an $eGFR_{crcys}$ $\geq$90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ (48.2%) or 60–$<$90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ (47.7%), whereas 4.1% had an $eGFR_{crcys}$ $<$60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$. Median UAE was 6.7 [IQR 4.1–11.9] mg/24 h. In 10.4% UAE was 15 to $<$30 mg/24 h, whereas it was $\geq$30 mg/24 h in 8.6%. In general, participants with

**Table 1. Clinical characteristics of the study population stratified according to $eGFR_{crcys}$ categories.[a]**

| | | $eGFR_{crcys}$ categories | | | |
|---|---|---|---|---|---|
| | Study population, n = 3103 | ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, n = 1497 | 60 to <90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, n = 1480 | <60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, n = 126 | *P* value[b] |
| Demographics | | | | | |
| Age, years | 59.8 ± 8.2 | 56.5 ± 8.1 | 62.6 ± 7.1 | 67.2 ± 6.2 | <0.001 |
| Men | 1608 (51.8) | 763 (51.0) | 770 (52.0) | 75 (59.5) | 0.18 |
| Educational level | | | | | <0.001 |
| Low | 517 (16.7) | 207 (13.8) | 271 (18.3) | 39 (31.0) | |
| Intermediate | 1327 (42.8) | 664 (44.4) | 612 (41.4) | 51 (40.5) | |
| High | 1259 (40.6) | 626 (41.8) | 597 (40.3) | 36 (28.6) | |
| Ischemic ECG abnormalities | 333 (10.7) | 150 (10.0) | 157 (10.6) | 26 (20.6) | <0.01 |
| Questionnaire based prevalent cardiovascular disease[c] | 504 (16.5) | 186 (12.6) | 270 (18.6) | 48 (38.7) | <0.001 |
| Lifestyle variables | | | | | |
| Smoking behavior | | | | | 0.07 |
| Never smoker | 1088 (35.1) | 550 (36.7) | 507 (34.3) | 31 (24.6) | |
| Former smoker | 1596 (51.4) | 751 (50.2) | 772 (52.2) | 73 (57.9) | |
| Current smoker | 419 (13.5) | 196 (13.1) | 201 (13.6) | 22 (17.5) | |
| Alcohol consumption | | | | | <0.01 |
| None | 572 (18.4) | 269 (18.0) | 265 (17.9) | 38 (30.2) | |
| Low (women ≤7 glasses/week; men ≤14 glasses/week) | 1720 (55.4) | 827 (55.2) | 824 (55.7) | 69 (54.8) | |
| High (women >7 glasses/week; men >14 glasses/week) | 811 (26.1) | 401 (26.8) | 391 (26.4) | 19 (15.1) | |
| Metabolic variables | | | | | |
| Waist circumference, cm | | | | | |
| Men | 101.4 ± 11.9 | 99.8 ± 11.9 | 102.3 ± 11.4 | 109.3 ± 12.5 | <0.001 |
| Women | 89.9 ± 13.0 | 88.4 ± 12.7 | 91.1 ± 13.0 | 96.5 ± 13.5 | <0.001 |
| Office systolic pressure, mmHg | 135.1 ± 18.2 | 133.3 ± 17.4 | 136.3 ± 18.7 | 141.7 ± 19.5 | <0.001 |
| Office diastolic pressure, mmHg | 76.2 ± 9.9 | 76.1 ± 9.6 | 76.6 ± 10.0 | 74.5 ± 10.9 | 0.05 |
| 24-h Average ambulatory systolic pressure, mmHg[d] | 119.1 ± 11.8 | 118.5 ± 11.8 | 119.5 ± 11.8 | 121.1 ± 11.9 | 0.02 |
| 24-h Average ambulatory diastolic pressure, mmHg[d] | 73.5 ± 7.2 | 73.9 ± 7.1 | 73.4 ± 7.3 | 70.7 ± 6.7 | <0.001 |
| Hypertension | 1742 (56.1) | 735 (49.1) | 890 (60.1) | 117 (92.9) | <0.001 |
| Glucose metabolism status | | | | | <0.001 |
| Normal glucose metabolism | 1775 (57.2) | 916 (61.2) | 827 (55.9) | 32 (25.4) | |
| Impaired fasting glucose | 129 (4.2) | 62 (4.1) | 62 (4.2) | 5 (4.0) | |
| Impaired glucose tolerance | 341 (11.0) | 156 (10.4) | 174 (11.8) | 11 (8.7) | |
| T2DM | 858 (27.7) | 363 (24.2) | 417 (28.2) | 78 (61.9) | |
| Hb $A_{1c}$ (%)[e] | | | | | |
| Without T2DM | 5.5 ± 0.4 | 5.5 ± 0.4 | 5.6 ± 0.4 | 5.6 ± 0.4 | <0.001 |
| With T2DM | 6.9 ± 1.0 | 6.9 ± 1.1 | 6.9 ± 0.9 | 7.0 ± 1.0 | 0.47 |
| Total cholesterol, mg/dL | 202.7 ± 44.8 | 202.2 ± 43.9 | 204.8 ± 45.3 | 183.9 ± 44.8 | <0.001 |
| HDL cholesterol, mg/dL | | | | | |
| Men | 51.4 ± 14.5 | 52.6 ± 14.8 | 50.7 ± 14.3 | 45.1 ± 11.1 | <0.001 |
| Women | 67.2 ± 18.5 | 68.1 ± 18.6 | 66.8 ± 18.4 | 60.2 ± 17.1 | <0.01 |
| LDL cholesterol, mg/dL | 119.5 ± 40.0 | 119.1 ± 39.2 | 121.5 ± 40.2 | 102.2 ± 40.8 | <0.001 |
| Triglycerides, mg/dL | 107.2 (77.9–152.3) | 100.1 (72.6–143.5) | 110.7 (84.1–155.0) | 138.2 (98.3–203.3) | <0.001 |
| Total-to-HDL cholesterol ratio | 3.7 ± 1.2 | 3.6 ± 1.2 | 3.8 ± 1.2 | 3.8 ± 1.1 | <0.01 |

*Continued on page 891*

**Table 1. Clinical characteristics of the study population stratified according to $eGFR_{crcys}$ categories.** *(Continued from page 890)*

| | | $eGFR_{crcys}$ categories | | | |
|---|---|---|---|---|---|
| | Study population, n = 3103 | ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, n = 1497 | 60 to <90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, n = 1480 | <60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, n = 126 | *P* value[b] |
| Kidney function | | | | | |
| $eGFR_{crcys}$, mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ | 88.2 ± 14.8 | 99.2 (94.3–104.5) | 80.1 (73.6–85.6) | 53.0 (48.6–57.5) | <0.001 |
| $eGFR_{cr}$, mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ | 84.5 ± 13.9 | 94.5 (89.2–99.9) | 77.3 (70.8–83.9) | 53.8 (46.7–58.4) | <0.001 |
| $eGFR_{cys}$, mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ | 89.8 ± 16.5 | 102.4 (96.6–107.9) | 80.8 (73.1–87.9) | 52.6 (46.4–57.3) | <0.001 |
| UAE, mg/24 h | 6.7 (4.1–11.9) | 6.4 (3.9–10.7) | 6.7 (4.1–12.3) | 14.4 (7.0–68.6) | <0.001 |
| UAE categories | | | | | <0.001 |
| <15 mg/24 h | 2514 (81.0) | 1261 (84.2) | 1187 (80.2) | 66 (52.4) | |
| 15 to <30 mg/24 h | 323 (10.4) | 148 (9.9) | 156 (10.5) | 19 (15.1) | |
| ≥30 mg/24 h | 266 (8.6) | 88 (5.9) | 137 (9.3) | 41 (32.5) | |
| Medication | | | | | |
| Antihypertensive medication | 1223 (39.4) | 469 (31.3) | 641 (43.3) | 113 (89.7) | <0.001 |
| Renin–angiotensin system inhibitor | 927 (29.9) | 350 (23.4) | 480 (32.4) | 97 (77.0) | <0.001 |
| Lipid-modifying medication | 1104 (35.6) | 454 (30.3) | 561 (37.9) | 89 (70.6) | <0.001 |
| Cardiac biomarkers | | | | | |
| hs-cTnT, ng/L | 6.6 ± 6.1 | 5.1 ± 3.1 | 7.5 ± 7.3 | 13.8 ± 9.8 | <0.001 |
| | 5.4 (3.9–7.9) | 4.6 (3.2–6.5) | 6.0 (4.4–8.8) | 11.3 (7.3–17.2) | <0.001 |
| hs-cTnI, ng/L | 3.2 ± 9.1 | 2.5 ± 5.9 | 3.6 ± 11.6 | 5.4 ± 7.1 | <0.001 |
| | 1.9 (1.3–3.1) | 1.7 (1.1–2.6) | 2.1 (1.4–3.4) | 3.7 (2.5–5.5) | <0.001 |
| NT-proBNP, ng/L | 82.6 ± 133.2 | 60.5 ± 63.8 | 92.8 ± 140.2 | 225.6 ± 362.5 | <0.001 |
| | 50.9 (29.1–90.5) | 41.9 (23.9–73.4) | 57.6 (34.0–99.0) | 101.9 (58.6–243.3) | <0.001 |

[a] Data are presented as n (%), mean ± SD, or median (interquartile range). Conversion factors for units: Hb $A_{1c}$ in % to mmol/mol, 10.93 × Hb $A_{1c}$ (%) + 23.5; cholesterol in mg/dL to mmol, × 0.02586; triglycerides in mg/dL to mmol/L, × 0.01129.
[b] *P* values for the comparison of participants across the $eGFR_{crcys}$ categories were calculated with the one-way ANOVA test for normally distributed variables, the Kruskal–Wallis test for nonnormally distributed variables and the $\chi^2$ test for categorical variables.
[c] Data available for 3059 participants.
[d] Data available for 2749 participants.
[e] Data available for 3096 participants.

lower $eGFR_{crcys}$ and participants with higher UAE had a worse CVD risk profile. Further, lower $eGFR_{crcys}$ was accompanied by higher UAE and vice versa. Online Supplemental Fig. 1 shows the distribution of hs-cTnT and hs-cTnI. hs-cTnT was above the LoD in 55.6%; hs-cTnI was above the LoD in 49.3% (1.9 ng/L) to 80.2% (1.1 ng/L).

#### eGFR AND CARDIAC BIOMARKERS

Participants with lower $eGFR_{crcys}$ had higher hs-cTnT, hs-cTnI, and NT-proBNP (Table 1). After adjustment for potential confounders, and as compared with $eGFR_{crcys}$ ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, both $eGFR_{crcys}$ 60–<90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ and $eGFR_{crcys}$ <60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ remained associated with higher hs-cTnT, hs-cTnI, and NT-proBNP (Table 2, model 4a). Results were similar when we adjusted for 24-h average ambulatory systolic pressure (Table 2, model 4b).

When $eGFR_{crcys}$ was expressed as a continuous variable, each 10 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ lower $eGFR_{crcys}$ was associated with a [ratio (95% CI)] 1.11 (1.09–1.12) times higher hs-cTnT, a 1.07 (1.05–1.10) times higher hs-cTnI, and a 1.10 (1.08–1.13) times higher NT-proBNP (model 4a). However, these models somewhat underestimated the associations at lower $eGFR_{crcys}$ levels, particularly for NT-proBNP (Fig. 1).

#### eGFR AND CARDIAC BIOMARKERS—hs-cTnT VS hs-cTnI

The associations of categorical and continuous $eGFR_{crcys}$ with hs-cTnT were slightly stronger than those with hs-cTnI (Table 2, model 4a). This difference was statistically significant when we took their different distributions into account using a comparison of partial correlations in model 4a ($P$ <0.001 for $eGFR_{crcys}$ 60–<90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, $eGFR_{crcys}$ <60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$, and continuous $eGFR_{crcys}$).

**Table 2. Associations of $eGFR_{crcys}$ with biomarkers of cardiac injury.[a]**

| | | $eGFR_{crcys}$ ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ | | $eGFR^{crcys}$ 60 to <90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ | | $eGFR_{crcys}$ <60 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ | |
|---|---|---|---|---|---|---|---|
| Biomarker | Model | Ratio (95% CI) | *P* value | Ratio (95% CI) | *P* value | Ratio (95% CI) | *P* value |
| hs-cTnT | 1 | Reference | NA[b] | 1.44 (1.38–1.51) | <0.001 | 2.68 (2.40–3.00) | <0.001 |
| | 2 | Reference | NA | 1.23 (1.18–1.27) | <0.001 | 1.81 (1.65–1.99) | <0.001 |
| | 3 | Reference | NA | 1.21 (1.17–1.26) | <0.001 | 1.73 (1.57–1.90) | <0.001 |
| | 4a | Reference | NA | 1.21 (1.17–1.26) | <0.001 | 1.69 (1.53–1.85) | <0.001 |
| | 4b | Reference | NA | 1.21 (1.16–1.26) | <0.001 | 1.70 (1.54–1.88) | <0.001 |
| hs-cTnI | 1 | Reference | NA | 1.35 (1.27–1.43) | <0.001 | 2.24 (1.93–2.60) | <0.001 |
| | 2 | Reference | NA | 1.15 (1.09–1.22) | <0.001 | 1.63 (1.42–1.88) | <0.001 |
| | 3 | Reference | NA | 1.13 (1.07–1.19) | <0.001 | 1.49 (1.29–1.72) | <0.001 |
| | 4a | Reference | NA | 1.14 (1.07–1.20) | <0.001 | 1.45 (1.26–1.66) | <0.001 |
| | 4b | Reference | NA | 1.15 (1.08–1.22) | <0.001 | 1.45 (1.25–1.68) | <0.001 |
| NT-proBNP | 1 | Reference | NA | 1.40 (1.32–1.50) | <0.001 | 2.82 (2.39–3.33) | <0.001 |
| | 2 | Reference | NA | 1.17 (1.09–1.25) | <0.001 | 2.15 (1.82–2.54) | <0.001 |
| | 3 | Reference | NA | 1.19 (1.11–1.27) | <0.001 | 2.05 (1.74–2.43) | <0.001 |
| | 4a | Reference | NA | 1.19 (1.12–1.27) | <0.001 | 1.94 (1.64–2.29) | <0.001 |
| | 4b | Reference | NA | 1.19 (1.11–1.28) | <0.001 | 1.97 (1.65–2.34) | <0.001 |

[a] Betas represent the ratio of geometric mean concentrations of cardiac biomarkers in the respective $eGFR_{crcys}$ category relative to participants with an $eGFR_{crcys}$ ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$. Model 1: unadjusted model; model 2: age, sex, glucose metabolism status; model 3: model 2 + waist circumference, total-to-HDL cholesterol ratio, triglycerides, use of lipid-modifying medication, smoking behavior, alcohol consumption, educational level, UAE (categorical); model 4a: model 3 + office systolic pressure, use of antihypertensive medication, ischemic ECG abnormalities; model 4b: similar to model 4a but adjusted for 24-h average ambulatory systolic pressure instead of office systolic pressure (missing in 354 participants).

[b] NA, not applicable.

### ALBUMINURIA AND CARDIAC BIOMARKERS

Participants with higher UAE had higher hs-cTnT, hs-cTnI, and NT-proBNP (see online Supplemental Table 1). After adjustment for potential confounders, and as compared with UAE <15 mg/24 h, both UAE 15–<30 mg/24 h and UAE ≥30 mg/24 h remained associated with higher hs-cTnI, whereas only UAE ≥30 mg/24 h was associated with higher hs-cTnT and NT-proBNP

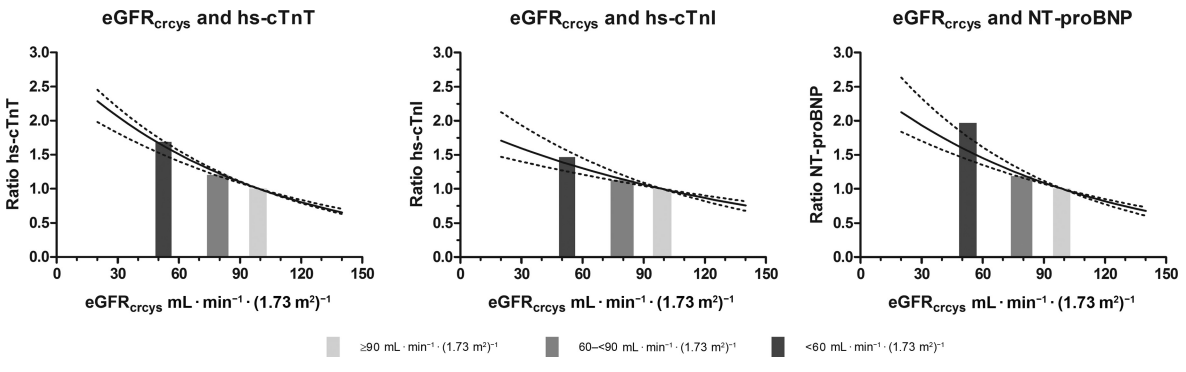


**Fig. 1. Associations of $eGFR_{crcys}$ with hs-cTnT (left panel), hs-cTnI (middle panel), and NT-proBNP (right panel), for $eGFR_{crcys}$ expressed as a continuous variable (continuous lines with dashed lines for 95% CIs) and as a categorical variable (columns).**

Columns for $eGFR_{crcys}$ categories were set at the median $eGFR_{crcys}$ value of the respective category (column width represents IQR). Ratios represent the ratio of geometric mean concentrations of cardiac biomarkers as compared with an $eGFR_{crcys}$ of 99.2 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ [the median $eGFR_{crcys}$ in participants with $eGFR_{crcys}$ ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$] for $eGFR_{crcys}$ expressed as a continuous variable or as compared with $eGFR_{crcys}$ ≥90 mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ for $eGFR_{crcys}$ expressed as a categorical variable (model 4a).

**Table 3. Associations of albuminuria with biomarkers of cardiac injury.[a]**

| | | UAE <15 mg/24 h | | UAE 15-<30 mg/24 h | | UAE ≥30 mg/24 h | |
|---|---|---|---|---|---|---|---|
| Biomarker | Model | Ratio (95% CI) | *P* value | Ratio (95% CI) | *P* value | Ratio (95% CI) | *P* value |
| hs-cTnT | 1 | Reference | NA[b] | 1.27 (1.19–1.37) | <0.001 | 1.69 (1.56–1.84) | <0.001 |
| | 2 | Reference | NA | 1.05 (0.99–1.12) | 0.10 | 1.22 (1.14–1.31) | <0.001 |
| | 3 | Reference | NA | 1.04 (0.98–1.10) | 0.21 | 1.13 (1.06–1.21) | <0.001 |
| | 4a | Reference | NA | 1.04 (0.98–1.10) | 0.23 | 1.11 (1.04–1.18) | <0.01 |
| | 4b | Reference | NA | 1.01 (0.95–1.08) | 0.67 | 1.09 (1.01–1.17) | 0.02 |
| hs-cTnI | 1 | Reference | NA | 1.27 (1.16–1.40) | <0.001 | 1.79 (1.61–1.98) | <0.001 |
| | 2 | Reference | NA | 1.11 (1.02–1.21) | 0.02 | 1.41 (1.28–1.55) | <0.001 |
| | 3 | Reference | NA | 1.10 (1.01–1.19) | 0.04 | 1.34 (1.21–1.47) | <0.001 |
| | 4a | Reference | NA | 1.08 (1.00–1.18) | 0.07 | 1.26 (1.14–1.38) | <0.001 |
| | 4b | Reference | NA | 1.07 (0.97–1.17) | 0.16 | 1.21 (1.09–1.34) | <0.001 |
| NT-proBNP | 1 | Reference | NA | 1.08 (0.97–1.21) | 0.15 | 1.51 (1.34–1.70) | <0.001 |
| | 2 | Reference | NA | 1.05 (0.95–1.17) | 0.32 | 1.52 (1.35–1.70) | <0.001 |
| | 3 | Reference | NA | 1.06 (0.96–1.17) | 0.28 | 1.41 (1.26–1.58) | <0.001 |
| | 4a | Reference | NA | 1.07 (0.96–1.18) | 0.21 | 1.34 (1.19–1.50) | <0.001 |
| | 4b | Reference | NA | 1.04 (0.94–1.16) | 0.43 | 1.29 (1.15–1.46) | <0.001 |

[a] Betas represent the ratio of geometric mean concentrations of cardiac biomarkers in the respective albuminuria category relative to participants with a UAE <15 mg/24 h. Model 1: unadjusted model; model 2: age, sex, glucose metabolism status; model 3: model 2 + waist circumference, total-to-HDL cholesterol ratio, triglycerides, use of lipid-modifying medication, smoking behavior, alcohol consumption, educational level, $eGFR_{crcys}$ (categorical); model 4a: model 3 + office systolic pressure, use of antihypertensive medication, ischemic ECG abnormalities; model 4b: similar to model 4a but adjusted for 24-h average ambulatory systolic pressure instead of office systolic pressure (missing in 354 participants).
[b] NA, not applicable.

(Table 3, model 4a). Results were similar when we adjusted for 24-h average ambulatory systolic pressure (Table 3, model 4b).

When albuminuria was expressed as a continuous variable, each doubling of UAE was associated with a [ratio (95% CI)] 1.03 (1.02–1.04) times higher hs-cTnT, a 1.05 (1.03 –1.07) times higher hs-cTnI, and a 1.07 (1.04–1.09) times higher NT-proBNP (model 4a). However, these models somewhat underestimated the associations at higher UAE, particularly for hs-cTnI and NT-proBNP (Fig. 2).

### ALBUMINURIA AND CARDIAC BIOMARKERS–hs-cTnT VS hs-cTnI

The associations of categorical and continuous albuminuria with hs-cTnI seemed to be slightly stronger than those with hs-cTnT (Table 3, model 4a), but this difference was not statistically significant when we took the distributions of hs-cTnT and hs-cTnI into account using a comparison of partial correlations in model 4a ($P$ = 0.57 for UAE 15–<30 mg/24 h; $P$ = 0.13 for UAE ≥30 mg/24 h; $P$ = 0.72 for continuous UAE).

### ADDITIONAL ANALYSES

First, results were not materially altered: when we restricted the analyses to participants with UAE ≤300 mg/24 h (n = 3081) or to participants with 2 urine collections (n = 2851); after additional adjustment for total (n = 2717) or moderate to vigorous physical activity (n = 2716), or questionnaire based prevalent CVD (n = 3059); when we replaced office systolic pressure with either office diastolic pressure, office pulse pressure, office mean arterial pressure or their 24-h average ambulatory equivalents, or the presence of hypertension; and when we replaced the use of antihypertensive medication with the use of a renin–angiotensin system inhibitor (data not shown). Second, when $eGFR_{crcys}$ was replaced with $eGFR_{cr}$, associations of eGFR with hs-cTnT and NT-proBNP became numerically weaker but remained statistically significant, whereas results were similar when $eGFR_{crcys}$ was replaced with $eGFR_{cys}$ (see online Supplemental Table 2). Third, analyses with interaction terms indicated statistically significant interaction ($P_{interaction}$ <0.10) between $eGFR_{crcys}$ and T2DM, to such an extent that the associations of $eGFR_{crcys}$ with the cardiac biomarkers were stronger in participants with T2DM than in participants with normal glucose metabolism (see stratified analyses in online Supplemental Table 3). In addition, the associations of albuminuria with NT-proBNP were stronger in participants with T2DM than in participants with normal glucose metabolism (see

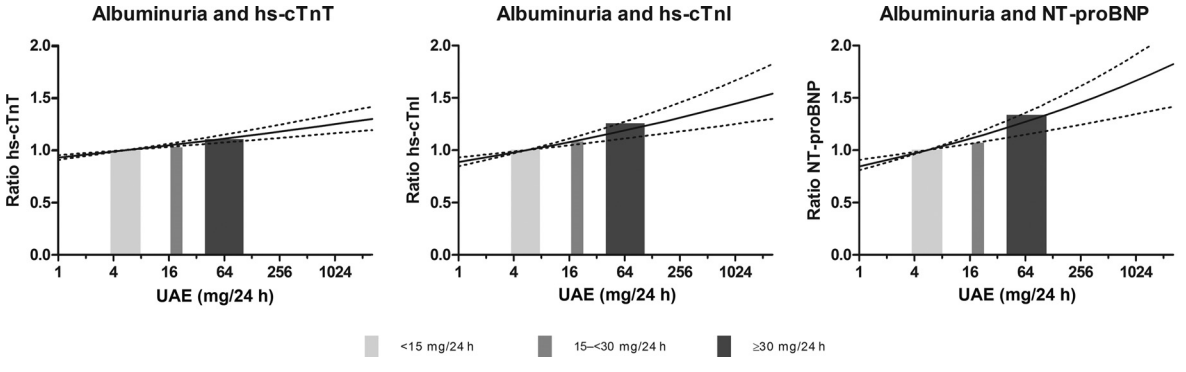


**Fig. 2. Associations of albuminuria with hs-cTnT (left panel), hs-cTnI (middle panel), and NT-proBNP (right panel), for albuminuria expressed as a continuous variable (continuous lines with dashed lines for 95% CIs) and as a categorical variable (columns).**

Columns for urinary albumin excretion categories were set at the median urinary albumin excretion of the respective category (column width approximates the IQR). Ratios represent the ratio of geometric mean concentrations of cardiac biomarkers as compared with a urinary albumin excretion of 5.6 mg/24 h (the median urinary albumin excretion in participants with a urinary albumin excretion <15 mg/24 h) for albuminuria expressed as a continuous variable or as compared with a urinary albumin excretion <15 mg/24 h for albuminuria expressed as a categorical variable (model 4a).

stratified analyses in online Supplemental Table 4). Fourth, UAE ≥30 mg/24 h, but none of the $eGFR_{crcys}$ categories, was positively associated with ischemic ECG abnormalities after adjustment for potential confounders (see online Supplemental Table 5).

## Discussion

This population-based study on the associations of eGFR and albuminuria with biomarkers of cardiac injury had two main findings. First, $eGFR_{crcys}$ and albuminuria were mutually independently associated with hs-cTnT, hs-cTnI, and NT-proBNP after adjustment for demographics, lifestyle variables, and CVD risk factors. Second, $eGFR_{crcys}$ was more strongly associated with hs-cTnT than with hs-cTnI. However, although statistically significant, this difference seemed modest in absolute terms. Of interest, for albuminuria the associations with hs-cTnT and hs-cTnI were much more similar.

Our results are in line with most *(5, 11, 13)* but not all *(12)* of the few previous studies that have conjointly evaluated eGFR and albuminuria and have shown mutually independent associations of both with hs-cTnT *(5, 11, 13)*, hs-cTnI *(5)*, and NT-proBNP *(11)*. The present study expands the population-based data on this topic *(11, 13)* by its direct comparison of both cTn and the detailed characterization of its population, which allowed adjustment for an extensive series of potential confounders, including 24-h average ambulatory blood pressure. Altogether, the available data argue that eGFR and albuminuria are, over their entire range, associated with these biomarkers of cardiac injury.

cTn are released following myocardial injury due to, for example, cardiac ischemia, and possibly also cardiac strain *(3)*. Similarly, NT-proBNP may be a marker of "pan-cardiac disease" *(4)*, being associated with left ventricular dysfunction, left ventricular hypertrophy, left atrial dilation, and cardiac ischemia *(4)*. NT-proBNP (8.5 kDa) is subsequently eliminated via the kidneys *(7)*, whereas the elimination routes of cTnT and cTnI are unknown. However, based on their molecular weight, free cTnT (37 kDa), free cTnI (24 kDa), and their fragments may be (partly) filtered by the glomeruli and catabolized by the tubules *(25, 26)*. Indeed, after myocardial infarction, cTnT and cTnI have been observed as free cTnT and cTnI, larger cTnT-I-C (77 kDa) and cTnI-C (40 kDa) complexes, and fragments *(27–31)*. In contrast, in renal failure, cTnT circulates primarily as fragments *(32)*, whereas the circulating form of cTnI in renal failure is unknown.

In this study, we could not determine the relative contributions of lower renal elimination and cardiac injury to the association of eGFR with the cardiac biomarkers. The observation that eGFR seemed to be associated more strongly with the biomarkers than albuminuria, the absence of a positive association with ischemic ECG abnormalities and the minor attenuation of the regression coefficients after adjustment for these ECG findings may indicate a role for lower renal elimination. However, the cardiac biomarkers may identify cardiac injury that is subclinical and not visible on an ECG. Further, findings from other studies strongly argue that cardiac injury is involved. First, eGFR has been associated with CVD mortality at concentrations ≥60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$, especially if the GFR esti-

mate included cystatin C *(2)*, and the evidence for an association of eGFR $<60$ mL · min$^{-1}$ · (1.73 m$^2$)$^{-1}$ with CVD is compelling *(1, 2)*. Second, hs-cTnT and NT-proBNP have been associated with incident overt CVD regardless of eGFR in the general population *(11)*. Therefore, the results of this study suggest that (subclinical) cardiac injury may be a mechanism for the CVD mortality risk associated with lower eGFR in the general population.

In this study, eGFR was associated with the cardiac biomarkers regardless of the filtration marker and equation used. Nevertheless, associations of eGFR with hs-cTnT and NT-proBNP were numerically stronger with GFR estimates that included cystatin C. This observation agrees with data on the association of eGFR with CVD mortality *(2)*. Non-GFR determinants of cystatin C, which may include obesity, diabetes, and inflammation, may have augmented the association with the cardiac biomarkers *(2)*. Alternatively, cystatin C may be a more sensitive biomarker of GFR than creatinine in populations with more comorbidities *(33)*.

The association of albuminuria with the biomarkers of cardiac injury, which was independent of its association with ischemic ECG abnormalities, fits the strong association of albuminuria with CVD mortality *(1)*. Generalized endothelial dysfunction and/or capillary rarefaction may explain the association of albuminuria with cardiac injury. According to this theory, endothelial dysfunction and capillary rarefaction in the microcirculation (i.e., microvascular dysfunction) of the kidneys leads to albuminuria *(8, 9)*, whereas in the heart both may cause a supply demand mismatch with (subclinical) ischemia *(10)*. Indeed, lower coronary flow reserve *(34)* and lower myocardial perfusion reserve *(35)*, which are measures of microvascular dysfunction of the heart *(10)*, have been associated with higher cTn *(34)* and NT-proBNP *(35)* in individuals without overt coronary artery disease. Importantly, albuminuria has also been associated with lower coronary flow reserve *(36)*.

Explorative analyses suggested that the associations of eGFR with hs-cTnT, hs-cTnI, and NT-proBNP, and the association of albuminuria with NT-proBNP, were stronger in individuals with T2DM. Although speculative, these observations may have several explanations. First, the diabetic milieu may augment the effects of reduced eGFR on CVD. Second, experimental data suggest that albuminuria could be a better biomarker of microvascular disease in individuals with diabetes than in nondiabetic individuals *(37, 38)*. This may be because hyperglycemia may disrupt the vascular endothelial growth factor (VEGF)–nitric oxide (NO) axis and, thereby, may aggravate vascular injury *(39)*. Alternatively or additionally, in individuals with T2DM, glomerular hyperfiltration *(40)* may increase permeation of albumin through an injured glomerular capillary wall. Third, for NT-proBNP the interaction with T2DM may reflect the distributions of eGFR and UAE according to glucose metabolism status (i.e., lower eGFR and higher UAE in individuals with T2DM), combined with curvilinear associations of both with NT-proBNP (Figs. 1 and 2). Nevertheless, we cannot exclude the play of chance.

Our finding that eGFR was more strongly associated with hs-cTnT than hs-cTnI expands the results of studies in selected populations *(5, 14–19)* to the range of eGFR observed in the general population. Differences in renal elimination between both cTn, for example accumulation of cTnT fragments *(32)*, may explain their differential association with eGFR *(15)*. However, other explanations should also be considered. For example, differences in stability and modification after release into the circulation that interfere with detection may exist in the face of reduced eGFR *(41)*. Hence, future mechanistic studies should compare the extent of renal elimination of cTnT and cTnI. The similar associations of albuminuria with both cTn disagree with a smaller study that also showed stronger associations of albuminuria with hs-cTnT than hs-cTnI *(5)*. However, that study did not formally compare both cTn taking their different distributions into account.

Our study had some limitations. First, owing to the cross-sectional design and the absence of data on hard clinical outcomes, such as incident CVD, we cannot make strong causal inferences and we cannot determine the direction of the associations. In fact, these may be bidirectional *(42, 43)*. In addition, data on hard clinical outcomes may clarify the clinical relevance of the differences between hs-cTnT and hs-cTnI. Second, although we measured cTnT and cTnI with hs assays, concentrations were still below the LoB and LoD in a substantial number of participants. Third, the lack of standardization of hs-cTnI assays may hamper generalizability to other hs-cTnI assays. Fourth, participants resided in a single region in the Netherlands, and the vast majority were white individuals from European descent (98.6%); this may limit generalizability to other ethnic groups.

In conclusion, eGFR and albuminuria were, independently of each other, associated with biomarkers of (subclinical) cardiac injury, and these associations already appeared at levels that do not fulfill the CKD criteria. Although reduced renal elimination may partly underlie the associations of eGFR, this study supports the concept that eGFR and albuminuria are, over their entire range, associated with cardiac injury. In addition, eGFR was more strongly associated with hs-cTnT than with hs-cTnI. The mechanisms responsible for this difference need further study as this could be of clinical relevance.

**Author Contributions:** *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisi-*

*tion of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

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## References


1. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–73.
2. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369:932–43.
3. Giannitsis E, Katus HA. Cardiac troponin level elevations not related to acute coronary syndromes. Nat Rev Cardiol 2013;10:623–34.
4. Struthers A, Lang C. The potential to improve primary prevention in the future by using BNP/N-BNP as an indicator of silent 'pancardiac' target organ damage: BNP/N-BNP could become for the heart what microalbuminuria is for the kidney. Eur Heart J 2007;28:1678–82.
5. deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, et al. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. Clin Chem 2012;58:1342–51.
6. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation 2007;116:85–97.
7. van Kimmenade RR, Januzzi JL Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, et al. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. J Am Coll Cardiol 2009;53:884–90.
8. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. J Am Soc Nephrol 2006;17:2106–11.
9. Martens RJ, Henry RM, Houben AJ, van der Kallen CJ, Kroon AA, Schalkwijk CG, et al. Capillary rarefaction associates with albuminuria: the Maastricht Study. J Am Soc Nephrol 2016;27:3748–57.
10. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.
11. Scheven L, de Jong PE, Hillege HL, Lambers Heerspink HJ, van Pelt LJ, Kootstra JE, et al. 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. Eur Heart J 2012;33:2272–81.
12. Dubin RF, Li Y, He J, Jaar BG, Kallem R, Lash JP, et al. Predictors of high sensitivity cardiac troponin T in chronic kidney disease patients: a cross-sectional study in the Chronic Renal Insufficiency Cohort (CRIC). BMC Nephrol 2013;14:229.
13. Xiao W, Ye P, Cao R, Yang X, Bai Y, Wu H. Urine albumin excretion is associated with cardiac troponin T detected with a highly sensitive assay in a community-based population. PloS one 2015;10:e0135747.
14. Guclu T, Bolat S, Senes M, Yucel D. Relationship between high sensitivity troponins and estimated glomerular filtration rate. Clin Biochem 2016;49:467–71.
15. Cardinaels EP, Daamen MA, Bekers O, Ten Kate J, Niens M, van Suijlen JD, et al. Clinical interpretation of elevated concentrations of cardiac troponin T, but not troponin I, in nursing home residents. J Am Med Dir Assoc 2015;16:884–91.
16. Lamb EJ, Kenny C, Abbas NA, John RI, Webb MC, Price CP, Vickery S. Cardiac troponin I concentration is commonly increased in nondialysis patients with CKD: experience with a sensitive assay. Am J Kidney Dis 2007;49:507–16.
17. Lippi G, Cervellin G. High-sensitivity troponin T is more susceptible than high-sensitivity troponin I to impaired renal function. Am J Cardiol 2013;112:1985.
18. Abbas NA, John RI, Webb MC, Kempson ME, Potter AN, Price CP, et al. Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. Clin Chem 2005;51:2059–66.
19. Bjurman C, Petzold M, Venge P, Farbemo J, Fu ML, Hammarsten O. High-sensitive cardiac troponin, NT-proBNP, hFABP and copeptin levels in relation to glomerular filtration rates and a medical record of cardiovascular disease. Clin Biochem 2015;48:302–7.
20. Schram MT, Sep SJ, van der Kallen CJ, Dagnelie PC, Koster A, Schaper N, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. Eur J Epidemiol 2014;29:439–51.
21. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.
22. Spauwen PJ, van Boxtel MP, Verhey FR, Kohler S, Sep SJ, Koster A, et al. Both low and high 24-hour diastolic blood pressure are associated with worse cognitive performance in type 2 diabetes: The Maastricht Study. Diabetes Care 2015;38:1473–80.
23. Steiger JH. Tests for comparing elements of a correlation matrix. Psychol Bull 1980;87:245–51.
24. van Sloten TT, Henry RM, Dekker JM, Nijpels G, Unger T, Schram MT, Stehouwer CD. Endothelial dysfunction plays a key role in increasing cardiovascular risk in type 2 diabetes: The Hoorn study. Hypertension 2014;64:1299–305.
25. Carone FA, Peterson DR, Oparil S, Pullman TN. Renal tubular transport and catabolism of proteins and peptides. Kidney Int 1979;16:271–8.
26. Maack T, Johnson V, Kau ST, Figueiredo J, Sigulem D. Renal filtration, transport, and metabolism of low-molecular-weight proteins: a review. Kidney Int 1979;16:251–70.
27. Wu AH, Feng YJ, Moore R, Apple FS, McPherson PH, Buechler KF, Bodor G. Characterization of cardiac troponin subunit release into serum after acute myocardial infarction and comparison of assays for troponin T and I. American Association for Clinical Chemistry subcommittee on cTnI standardization. Clin Chem 1998;44:1198–208.
28. Cardinaels EP, Mingels AM, van Rooij T, Collinson PO, Prinzen FW, van Dieijen-Visser MP. Time-dependent degradation pattern of cardiac troponin T following myocardial infarction. Clin Chem 2013;59:1083–90.
29. Labugger R, Organ L, Collier C, Atar D, Van Eyk JE. Extensive troponin I and T modification detected in serum from patients with acute myocardial infarction. Circulation 2000;102:1221–6.
30. Peronnet E, Becquart L, Poirier F, Cubizolles M, Choquet-Kastylevsky G, Jolivet-Reynaud C. SELDI-TOF MS analysis of the cardiac troponin I forms present in plasma from patients with myocardial infarction. Proteomics 2006;6:6288–99.
31. Katrukha AG, Bereznikova AV, Esakova TV, Pettersson K, Lovgren T, Severina ME, et al. Troponin I is released in bloodstream of patients with acute myocardial infarction not in free form but as complex. Clin Chem 1997;43:1379–85.
32. Mingels AM, Cardinaels EP, Broers NJ, Van Sleeuwen A, Streng AS, Van Dieijen-Visser MP, et al. Cardiac troponin T: smaller molecules in patients with end-stage renal disease than after onset of acute myocardial infarction. Clin Chem 2017;63:683–90.
33. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C:

incorporation into clinical practice. Am J Kidney Dis 2013;62:595–603.
**34.** Taqueti VR, Everett BM, Murthy VL, Gaber M, Foster CR, Hainer J, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation 2015;131:528–35.
**35.** Mitchell A, Misialek JR, Folsom AR, Duprez D, Alonso A, Jerosch-Herold M, et al. Usefulness of N-terminal probrain natriuretic peptide and myocardial perfusion in asymptomatic adults (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol 2015;115:1341–5.
**36.** von Scholten BJ, Hasbak P, Christensen TE, Ghotbi AA, Kjaer A, Rossing P, Hansen TW. Cardiac (82)Rb PET/CT for fast and non-invasive assessment of microvascular function and structure in asymptomatic patients with type 2 diabetes. Diabetologia 2016;59:371–8.
**37.** Zhao HJ, Wang S, Cheng H, Zhang MZ, Takahashi T, Fogo AB, et al. Endothelial nitric oxide synthase deficiency produces accelerated nephropathy in diabetic mice. J Am Soc Nephrol 2006;17:2664–9.
**38.** Nakagawa T, Sato W, Glushakova O, Heinig M, Clarke T, Campbell-Thompson M, et al. Diabetic endothelial nitric oxide synthase knockout mice develop advanced diabetic nephropathy. J Am Soc Nephrol 2007;18:539–50.
**39.** Nakagawa T. Uncoupling of the VEGF-endothelial nitric oxide axis in diabetic nephropathy: an explanation for the paradoxical effects of VEGF in renal disease. Am J Physiol Renal Physiol 2007;292:F1665–72.
**40.** Vora JP, Dolben J, Dean JD, Thomas D, Williams JD, Owens DR, Peters JR. Renal hemodynamics in newly presenting non-insulin dependent diabetes mellitus. Kidney Int 1992;41:829–35.
**41.** Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 2002;40:2065–71.
**42.** Bansal N, Katz R, Dalrymple L, de Boer I, DeFilippi C, Kestenbaum B, et al. NT-proBNP and troponin T and risk of rapid kidney function decline and incident CKD in elderly adults. Clin J Am Soc Nephrol 2015;10:205–14.
**43.** Ho JE, Hwang SJ, Wollert KC, Larson MG, Cheng S, Kempf T, et al. Biomarkers of cardiovascular stress and incident chronic kidney disease. Clin Chem 2013;59:1613–20.