Estimated glomerular filtration rate, urine albumin excretion, and survival among patients consulting in public Chilean public primary care clinics

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ABSTRACT
Chronic renal disease (CRD) in its pre-dialysis stage is an important risk factor for mortality among adults. The aim of this study was to assess the effects of CRD on mortality among consultants in Chilean public primary care clinics. We obtained information about serum creatinine, urinary albumin excretion (UAE), blood pressure, and body mass index of 5224 consultants [3379 females aged 67 (59–75) years and 1845 males aged 68 (59–75) years] in three clinics of Metropolitan Santiago. Kaplan–Meier curves and Cox proportional hazard regression models were used to determine risk factors for mortality, determined 41 months after obtaining the blood samples. During the follow-up period, 262 patients died (33% due to circulatory causes and 29% due to tumors). Kaplan–Meier curves showed that there was a significant association between survival, estimated glomerular filtration rate, and UAE. Cox models showed that serum creatinine, UAE, a lower body mass index, and a history of diabetes were significant mortality predictors. A sensitivity analysis performed eliminating extreme ages (less than 50 and more than 80 years), included high diastolic pressure as a predictor of survival. We conclude that among patients with CRD in its pre-dialysis stage, UAE is an important predictor of survival, along with serum creatinine. A low body mass index was associated with a higher mortality.

Introduction
Chronic renal disease (CRD) refers to a reduction of renal function lasting more than three months that is irreversible and tends to progress over time. Its prevalence worldwide is 8–16\textsuperscript{1} and 12.1% in primary urban health care clinics in Chile.\textsuperscript{2} Although only 1% of these patients will require dialysis or transplantation, the disease burden of this condition is determined by the high costs of renal replacement therapies and the higher risk of mortality that it implies.\textsuperscript{3} The risk of cardiovascular disease increases by a factor of two to four among patients with CRD.\textsuperscript{4} Although the disease is progressive, its timely detection allows the use of interventions that reduce the rate of progression such as renin-angiotensin system inhibitors, sodium or protein intake reduction.\textsuperscript{5} The diagnosis and classification of CRD depend on the measurement of serum creatinine and urinary albumin excretion (UAE). Several formulas are used to estimated glomerular filtration rate (eGFR) using creatinine levels, such as the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CRD-EPI). This last formula is considered nowadays as the most accurate.\textsuperscript{6} UAE, initially considered as a marker of diabetic nephropathy, is another important tool for the diagnosis of CRD. It is an indicator of proximal tubular dysfunction,\textsuperscript{7} is an independent predictor of mortality, and is closely related to inflammation\textsuperscript{8} and general vascular damage.\textsuperscript{9} Thus, it complements the prediction of risk conferred by glomerular filtration rate.

Several reports have addressed the separate importance of eGFR and UAE to determine cardiovascular risk. A meta-analysis of Matsuchita et al. showed a linear and non-interacting increase in the risk of general and cardiovascular mortality associated with eGFR values below 60 mL/min/1.73 m\textsuperscript{2} and UAE over 10 mg/g creatinine. The risk associated with increased UAE was higher than that associated to reduced eGFR.\textsuperscript{10} Therefore, it is worth exploring the mortality risk associated with a low eGFR and increased UAE in a low-middle income country, not included in the published meta-analyses, which may behave differently. Also, comparing the mortality risk associated with CRD with the risk conferred by traditional risk factors and history of previous cardiovascular events would provide useful information.
Material and methods

Subjects

We obtained information from 5269 consultants in three public primary health care clinics of Eastern Santiago aged 50 years or more, about all creatinine and UAE measurements made to them during 2009. Using the date in which the blood and urine samples were obtained, we retrieved clinical data of patients from their electronic medical records. To avoid confusions, we used data obtained from consultations within 30 days of obtaining the blood and urine sample.

Predictors and variables

The retrieved information considered the diagnoses of diabetes and hypertension, the history of smoking, acute myocardial infarction, or stroke. We also retrieved data about weight, height, and blood pressure. A group of patients had also the measurement of waist circumference. eGFR was calculated using the CRD-EPI formula and the stages of CRD were determined according to the classification proposed by KDIGO.\(^3\) Patients with end-stage renal disease (stage 5 renal failure) were excluded from analysis. UAE was expressed in mg/g creatinine and classified in three groups according to the above-mentioned proposal.\(^3\)

Outcome

Data about deaths that may have occurred in this group of patients at 31 December 2012, were requested to the National Identification Service, obtaining information about date and causes of eventual deaths, classified according to the International Statistical Classification of Diseases and Related Health Problems, tenth edition\(^{11}\) (ICD-10). With this information, we excluded patients who died within six months of the baseline assessment.

Ethics

Once the laboratory and clinical data were merged and death information was incorporated, we removed all identification means from the database to avoid confidentiality issues. This study was approved by the Institutional Review Board of the Eastern Metropolitan Health Service of Santiago, Chile.

Statistical analysis

Survival analysis was carried out using Kaplan–Meier curves. For multivariate survival analysis, Cox proportional hazards regression models were used, where eGFR and UAE were introduced as numerical variables. The other variables included in the models were age, sex, history of myocardial infarction, stroke, hypertension, diabetes mellitus, systolic and diastolic blood pressures, and body mass index. In an alternative model, eGFR was replaced by serum creatinine levels. A sensitivity analysis was done eliminating subjects aged less than 50 or more than 80 years, and only including patients with measurement of waist circumference.

As most variables had a non-normal distribution, they are expressed as median (interquartile range). Differences between groups were calculated using Kruskal–Wallis ANOVA test. Differences in proportions were analyzed using $\chi^2$ tests. Differences in survival in Kaplan–Meier curves were analyzed testing log-ranks for equality. A stratified analysis was done comparing each stage of eGFR or UAE with the rest of groups to find out where resided the significant differences in survival. All statistical analyses were done in Stata for Windows version 12 (StataCorp LP, College Station, TX).

Results

Forty-five patients died within six months of the baseline evaluation and were discarded from further analysis. Thus, we analyzed 5224 patients, 3379 females aged 67 (59–75) years and 1845 males aged 68 (59–75) years. The follow-up period lasted 1263 days (41 months), during which 262 patients died. The causes of death were circulatory in 33%, tumors in 29%, gastrointestinal in 10%, and miscellaneous in the rest. The clinical and renal function features of patients who survived and those who died are shown in Table 1. Compared with deceased subjects, survivors had a significantly lower proportion of stroke history, a higher body mass index and a higher diastolic pressure. Clinical data, according to stages of eGFR and UAE, are shown in Table 2. Patients with higher stages of eGFR were older, had a lower BMI, and a lower frequency of smoking. They also had a higher frequency of myocardial infarction, stroke, hypertension, and diabetes histories. Patients with higher stages of UAE had higher systolic blood pressure and more frequently had a history of stroke, hypertension, and diabetes mellitus.

There was a significant correlation between age, serum creatinine, or eGFR (0.22 and $-0.51$ respectively, $p<0.01$). There was no significant association between UAE and age. Kaplan–Meier curves of survival are shown in Figures 1 and 2. As expected there was a significant association between survival, eGFR, and UAE. Stratified analysis showed that survival of all groups differed significantly between each other ($p<0.01$).
The Cox model including eGFR showed that UAE, age, body mass index, and a history of diabetes were significant independent predictors of survival. If eGFR was replaced by serum creatinine, this last parameter also became a significant predictor of survival. When subjects aged less than 50 years and more than 80 years were eliminated and serum creatinine was incorporated, a higher diastolic blood pressure became a significant predictor of survival. In only one model (which excluded extreme ages and incorporated serum creatinine), UAE lost significance as survival predictor (Table 3). When waist circumference (measured in 3703 patients) was incorporated to the cox models, it had no significant predictive effect on survival.

**Discussion**

These results confirm previous reports showing that serum creatinine and UAE are significant independent predictors of survival among adults. According to the multiple regression models, it appears that UAE is a stronger predictor than serum creatinine since only in one model, it lost significance. Creatinine is influenced by age.\(^{12,13}\) It is not surprising that eGFR shows a stronger association with age since the formula for calculation includes this parameter. Therefore, it is complicated to avoid the obvious confounding effect of age on survival in multivariate models. In fact, eGFR did not have a significant influence on survival in the Cox model, probably because its calculation includes age, a strong predictor of mortality, thus nullifying the effect of creatinine.

In this sample, the frequency of an eGFR below 60 mL/min/1.73 m\(^2\), considered as criteria for chronic kidney disease, was 26.3%, similar to the frequency reported by Cipullo in Brazil (23.4%) and lower than the frequency reported by Amato in Mexico (35.8%).\(^1\) However, the rates found in our study may be biased since this was an aged population consulting in a primary care clinic and not a random sample of healthy subjects of the community.

Since UAE was not influenced by age in this sample, it appears as a better predictor of survival among these two markers of CRD. Renal failure is strongly associated with endothelial surface layer lesions\(^{14}\) and there is an association between microalbuminuria and impaired flow-dependent vasodilation, suggesting endothelial dysfunction.\(^{15}\) In experimental animals, the enzymatic disruption of the endothelial surface layer increases microvascular permeability to albumin,\(^{16,17}\) alters flow-mediated vasodilation\(^{18}\) and allows the entry of low density lipoproteins to the vessel wall, accelerating the generation of atheroma.\(^{19}\) Thus, UAE surpasses its role as a marker of CRD and becomes another indicator of generalized vascular damage. In fact, when patients with moderate cardiovascular risk are stratified using UAE, the prediction of future cardiovascular events improves significantly.\(^{20}\) Probably, UAE will be incorporated as a parameter that has a greater strength than eGFR, to the calculations of cardiovascular risk.\(^{21}\) The low odds ratios of UAE in the regression models is a mathematical rather than a biological problem. Since UAE in these patients fluctuated from 0 to 3100, the change in risk per unit UAE change must be

**Table 1. Features of studied patients.**

| Feature                                | Total (n = 5224) | Survivors (n = 4962) | Deceased (n = 262) | p-Values* |
|----------------------------------------|------------------|----------------------|--------------------|-----------|
| Female/male                            | 3379/1845\(^5\)  | 3241/1721            | 138/124            | <0.01     |
| Age (years)                            | 67 (59–75)\(^6\) | 67 (59–75)           | 78 (70–83)         | <0.01     |
| Smoking                                | 355 (6.8%)\(^7\) | 342 (6.9%)           | 13 (5%)            | NS        |
| History of acute myocardial infarction | 260 (5%)         | 244 (4.9%)           | 16 (6.1%)          | NS        |
| History of stroke                      | 233 (4.3%)       | 210 (4.2%)           | 23 (8.8%)          | <0.01     |
| History of diabetes                    | 1890 (36.2%)     | 1784 (36%)           | 106 (40.5%)        | NS        |
| History of hypertension                | 4269 (81.7%)     | 4049 (81.6%)         | 220 (84%)          | NS        |
| Body mass index (kg/m\(^2\))           | 28.7 (25.8–32.1) | 28.7 (25.9–32.2)     | 26.6 (23.8–29.6)   | <0.01     |
| Systolic blood pressure (mmHg)         | 130 (120–140)    | 130 (120–140)        | 130 (111–140)      | NS        |
| Diastolic blood pressure (mmHg)        | 80 (70–85)       | 80 (70–85)           | 70 (70–80)         | <0.01     |
| Renal disease stage                    |                  |                      |                    |           |
| 1 (>90 mL/min/1.73m\(^2\))             | 907 (17.4%)      | 886 (17.9%)          | 21 (8.0%)          |           |
| 2 (60–89 mL/min/1.73m\(^2\))           | 2941 (56.3%)     | 2818 (56.8%)         | 123 (46.9%)        |           |
| 3a (45–59 mL/min/1.73m\(^2\))          | 1006 (19.3%)     | 938 (18.9%)          | 68 (26%)           |           |
| 3b (30–44 mL/min/1.73m\(^2\))          | 316 (6%)         | 281 (5.7%)           | 35 (13.4%)         |           |
| 4 (15–29 mL/min/1.73m\(^2\))           | 54 (1%)          | 39 (0.8%)            | 15 (5.7%)          | <0.01     |
| Microalbuminuria stage                 |                  |                      |                    |           |
| 1 (<30 mg/g creatinine)                | 4552 (87.1%)     | 4330 (87.3%)         | 192 (73.3%)        |           |
| 2 (30–300 mg/g creatinine)             | 627 (12%)        | 567 (11.4%)          | 60 (22.9%)         |           |
| 3 (>300 mg/g creatinine)               | 75 (1.4%)        | 65 (1.3%)            | 10 (3.8%)          | <0.01     |

*Comparison between survivors and deceased patients.
\(^{1}\)Number of observations.
\(^{2}\)Median (interquartile range).
\(^{3}\)Number of observations (percentage of observations).
Table 2. Clinical features of patients according to stages of kidney disease.

| Estimated glomerular filtration rate stage (eGFR) | 1          | 2          | 3a         | 3b         | 4          | p-Values<sup>a</sup> |
|-------------------------------------------------|------------|------------|------------|------------|------------|----------------------|
| **Frequency of**                                |            |            |            |            |            |                      |
| Smoking                                         | 10.5<sup>b</sup> | 6.4        | 5.2        | 5.4        | 5.6        | <0.01               |
| History of myocardial infarction                | 3.3        | 4.6        | 6.8        | 7.0        | 9.3        | <0.01               |
| History of stroke                               | 2.3        | 4.0        | 6.3        | 8.9        | 5.6        | <0.01               |
| History of hypertension                         | 74.1       | 81.9       | 86.1       | 87.0       | 85.2       | <0.01               |
| History of diabetes mellitus                    | 43.3       | 34.0       | 35.5       | 36.7       | 44.4       | <0.01               |
| **Age (years)**                                 | 58 (51–65)<sup>c</sup> | 67 (59–74) | 74 (68–80) | 78 (71–83) | 76.5 (69–83) | All groups different |
| Body mass index (kg/m<sup>2</sup>)               | 29.4 (26.5–33.2) | 28.7 (25.7–32.1) | 28.2 (25.5–31.7) | 28.3 (24.8–31.2) | 27.4 (25–32.7) | Group 1 different from others |
| Systolic blood pressure (mmHg)                  | 130 (120–140) | 130 (120–140) | 130 (120–140) | 130 (120–150) | 130 (120–150) | NS                  |
| Diastolic blood pressure (mmHg)                 | 80 (70–70) | 80 (70–70) | 80 (70–70) | 80 (70–70) | 80 (70–70) | NS                  |

| Stages of urinary albumin excretion              | 1          | 2          | 3          | p-Values   |
|-------------------------------------------------|------------|------------|------------|------------|
| **Frequency (%) of**                            |            |            |            |            |
| Smoking                                         | 6.7        | 7.5        | 6.7        | NS         |
| History of myocardial infarction                | 4.7        | 6.2        | 10.7       | <0.02      |
| History of stroke                               | 4.0        | 6.9        | 9.5        | <0.01      |
| History of hypertension                         | 81.6       | 81.3       | 89.3       | NS         |
| History of diabetes mellitus                    | 33.9       | 48.8       | 68.0       | <0.01      |
| **Age (years)**                                 | 67 (59–75)<sup>b</sup> | 68 (60–77) | 65 (57–74) | Groups 2 and 3 different |
| Body mass index (kg/m<sup>2</sup>)               | 28.6 (25.8–32.1) | 29.2 (26.1–32.9) | 28.7 (25–31.9) | NS         |
| Systolic blood pressure (mmHg)                  | 130 (120–140) | 130 (120–140) | 140 (130–160) | Group 3 different from others |
| Diastolic blood pressure (mmHg)                 | 80 (70–84) | 80 (70–90) | 80 (80–90) | NS         |

<sup>a</sup>Probability for differences between groups (χ² or Kruskal–Wallis tests).

<sup>b</sup>Percentage.

<sup>c</sup>Median (interquartile range).
necessarily low. If UAE is expressed categorically as in the univariate analysis, the risk stratification sharpens.

Noteworthy is that the only factor in the clinical history of patients that was incorporated to most of the Cox regression models was the presence of diabetes mellitus, the main pathogenic background of increased UAE. Another interesting finding of this study is that a low BMI was associated with a lower survival in all multivariate models. This is not new, considering that the studied population was composed mostly by older people. Epidemiological studies have reported previously that a low BMI increases the mortality risk in this age group. Several authors have emphasized the predictive value of body shape rather than BMI, specially a high waist circumference, on mortality. Unfortunately, not all of our patients had waist circumference measurements. However, when we incorporated this parameter to the Cox model in the group of patients in whom it was measured, it did not appear as a significant predictor of survival. Other explanation for this observation is that patients with chronic debilitating diseases lose weight. Thus in these cases a low BMI is associated with a higher mortality.

Blood pressure had an erratic behavior in the multivariate analysis. In the model incorporating all patients it had no effect on survival. When extreme ages were eliminated, a low diastolic pressure was associated with a lower survival. The most obvious explanation for these strange behaviors if that most patients had a diagnosis of hypertension and were receiving antihypertensive medications, thus artificially modifying blood pressure values. However, the history of hypertension was not a predictor either. The other explanation is that the association of blood pressure and mortality in older people is not as tight as in their younger counterparts. While some reports show no association of blood pressure with mortality, others have found also that low blood pressure is associated with higher death rates and yet other authors have reported that low blood pressure is only a risk factor among those with a low gait speed. The clue to understand these apparently bizarre data is blood pressure lowering therapy. There is solid evidence showing that overtreatment of hypertension in older people is associated with a higher mortality, probably caused by an increased risk of falls and higher levels of cognitive impairment. In fact, for orthostatic hypotension, a clear indicator of overtreatment is associated with higher mortality rates in diabetic patients. Even more, some groups are recommending an increase in blood pressure targets for the treatment of hypertensive patients older than 60 years.

This study has several weaknesses that must be addressed. First of all, compared to large meta-analyses including millions of patients, our sample number is relatively low. However, it is homogeneous in terms of ethnic and socioeconomic background. We also had an important number of patients without measurements of waist circumference, but the Cox models did not change substantially when only patients with such measurement were analyzed. Finally, we did not have baseline measures of serum lipid levels and glycosylated hemoglobin and we did not have information about medications used. This information would have been of value to assess the interaction of other potential risk factors for mortality. In conclusion, the presence of CRD and specially UAE are predictors of survival in this group of patients composed mostly by older people, consulting in Chilean public primary care clinics.
Table 3. Cox proportional models of survival.

|                        | All patients | Excluding extreme ages (<50 and >80 years) |
|------------------------|--------------|------------------------------------------|
|                        | (n = 5224)   | (n = 4288)                               |
| Hazard ratio           |              |                                          |
| 95% CI                 |              |                                          |
| p                      |              |                                          |
| Models using estimated glomerular filtration rate (eGFR) | | |
| Age (years)            | 1.08         | 1.06                                     |
|                        | 1.07–1.1     | 1.04–1.09                                |
| Male gender            | 1.61         | 1.72                                     |
|                        | 1.26–2.07    | 1.26–2.38                                |
| eGFR (mL/min/1.73m²)   | 1.00         | 0.99                                     |
|                        | 0.99–1       | 0.98–1                                   |
| Urine albumin (mg/g creatinine) | 1.00 | 1.00                                     |
|                        | 1              | 1–1                                      |
| History of:            |              |                                          |
| Smoking                | 0.90         | 0.90                                     |
|                        | 0.51–1.58   | 0.47–1.70                                |
| Acute myocardial infarction | 0.88 | 1.23                                     |
|                        | 0.53–1.46   | 0.68–2.23                                |
| Stroke                 | 1.39        | 1.53                                     |
|                        | 0.9–2.15    | 0.86–2.73                                |
| Hypertension           | 0.93        | 0.92                                     |
|                        | 0.66–1.3    | 0.82–1.24                                |
| Diabetes mellitus      | 1.33        | 1.38                                     |
|                        | 1.03–1.71   | 1.01–1.9                                 |
| Body mass index (kg/m²) | 0.94 | 0.95                                     |
|                        | 0.91–0.97   | 0.91–0.98                                |
| Systolic blood pressure (mm Hg) | 1.00 | 1.00                                     |
|                        | 0.99–1.01   | 0.99–1.01                                |
| Diastolic blood pressure (mm Hg) | 0.99 | 0.97                                     |
|                        | 0.97–1      | 0.95–0.99                                |
| Models using serum creatinine | | |
| Age (years)            | 1.08         | 1.06                                     |
|                        | 1.07–1.1     | 1.04–1.09                                |
| Male gender            | 1.41         | 1.42                                     |
|                        | 1.08–1.84   | 1.01–1.99                                |
| Serum creatinine (mg/dL) | 1.74 | 2.22                                     |
|                        | 1.19–2.55   | 1.35–3.65                                |
| Urine albumin (mg/g creatinine) | 1.00 | 1.00                                     |
|                        | 1–1         | 1–1                                      |
| History of:            |              |                                          |
| Smoking                | 0.88        | 0.93                                     |
|                        | 0.5–1.55    | 0.49–1.77                                |
| Acute myocardial infarction | 0.88 | 1.20                                     |
|                        | 0.53–1.46   | 0.66–2.17                                |
| Stroke                 | 1.38        | 1.50                                     |
|                        | 0.89–2.13   | 0.84–2.67                                |
| Hypertension           | 0.92        | 0.81                                     |
|                        | 0.66–1.29   | 0.54–1.23                                |
| Diabetes mellitus      | 1.33        | 1.37                                     |
|                        | 1.03–1.71   | 1.18–2.32                                |
| Body mass index (kg/m²) | 0.94 | 0.95                                     |
|                        | 0.91–0.97   | 0.91–0.98                                |
| Systolic blood pressure | 1.00        | 1.00                                     |
|                        | 0.99–1.01   | 0.99–1.01                                |
| Diastolic blood pressure | 0.99 | 0.97                                     |
|                        | 0.97–1      | 0.95–0.99                                |

Declaraction of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: Global dimension and perspectives. Lancet. 2013;382:260–272.
2. Zúñiga SMC, Müller OH, Flores OM. [Prevalence of chronic kidney disease in subjects consulting in urban primary care clinics]. Rev Med Chil. 2011;139:1176–1184.
3. Inker LA, Astor BC, Fox CH, et al. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;83:136–150.
4. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. Lancet. 2013;382:339–352.
5. James M, Hemmelgarn B, Tonelli M. Early recognition and prevention of chronic kidney disease. Lancet. 2010;375:1296–1309.
6. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: A systematic review. JAMA. 2015;313:837–846.
7. Dickson LE, Wagner MC, Sandovall RM, Molitoris BA. The proximal tubule and albuminuria: Really! J Am Soc Nephrol. 2014;25:443–453.
8. Upadhyay A, Larson MG, Guo CY, et al. Inflammation, kidney function and albuminuria in the Framingham Offspring cohort. Nephrol Dial Transplant. 2011;26:920–926.
9. Viazzi F, Pontremoli R. Blood pressure, albuminuria and renal dysfunction: The ‘chicken or egg’ dilemma. Nephrol Dial Transplant. 2014;29:1453–1455.
10. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts. Lancet. 2010;375:2073–2081.
11. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th ed. Geneva: WHO; 1992.
12. Uemura O, Honda M, Matsuyama T, et al. Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: A multicenter study. Clin Exp Nephrol. 2011;15:694–699.
13. Hannemann A, Friedrich N, Dittmann K, et al. Age- and sex-specific reference limits for creatinine, cystatin C and the estimated glomerular filtration rate. Clin Chem Lab Med. 2011;50:919–926.
14. Dane MJ, Khairoun M, Lee DH, et al. Association of kidney function with changes in the endothelial surface layer. Clin J Am Soc Nephrol. 2014;9:698–704.
15. Ito H, Nakashima M, Meguro K, et al. Flow mediated dilatation is reduced with the progressive stages of glomerular filtration rate and albuminuria in type 2 diabetic patients without coronary heart disease. J Diabetes Res. 2015;2015:728127.
16. Dane MJ, van den Berg BM, Avramut MC, et al. Glomerular endothelial surface layer acts as a barrier against albumin filtration. Am J Pathol. 2013;182:1532–1540.
17. Salmon AH, Ferguson JK, Burford JL, et al. Loss of the endothelial glycocalyx links albuminuria and vascular dysfunction. *J Am Soc Nephrol*. 2012;23:1339–1350.

18. Kumagai R, Lu X, Kassab GS. Role of glycocalyx in flow-induced production of nitric oxide and reactive oxygen species. *Free Radic Biol Med*. 2009;47:600–607.

19. Nagy N, Freudenberger T, Melchior-Becker A, et al. Inhibition of hyaluronan synthesis accelerates murine atherosclerosis: Novel insights into the role of hyaluronan synthesis. *Circulation*. 2010;122:2313–2322.

20. Greve SV, Blicher MK, Sehested T, et al. Effective risk stratification in patients with moderate cardiovascular risk using albuminuria and atherosclerotic plaques in the carotid arteries. *J Hypertens*. 2015;33:1563–1570.

21. Matsushita K, Coresh J, Sang Y, et al. CRD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: A collaborative meta-analysis of individual participant data. *Lancet Diab Endocrinol*. 2015;3:514–525.

22. Siddiqi FS, Advani A. Endothelial-podocyte crosstalk: The missing link between endothelial dysfunction and albuminuria in diabetes. *Diabetes*. 2013;62:3647–3655.

23. Corrada MM1, Kawas CH, Mozaffar F, Paganini-Hill A. Association of body mass index and weight change with all-cause mortality in the elderly. *Am J Epidemiol*. 2006;163:938–949.

24. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: Elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr*. 2006;84:449–460.

25. de Hollander EL, Bemelmans WJ, Boshuizen HC, et al. The association between waist circumference and risk of mortality considering body mass index in 65- to 74-year-olds: A meta-analysis of 29 cohorts involving more than 58 000 elderly persons. *Int J Epidemiol*. 2012;41:805–817.

26. Hepple RT. Muscle atrophy is not always sarcopenia. *J Appl Physiol*. 2012;113:677–679.

27. Lohr JW, Golzy M, Carter RL, Arora P. Elevated systolic blood pressure is associated with increased incidence of chronic kidney disease but not mortality in elderly veterans. *J Am Soc Hypertens*. 2015;9:29–37.

28. van Hateren KJ1, Landman GW, Kleefstra N, et al. Lower blood pressure associated with higher mortality in elderly diabetic patients (ZODIAC-12). *Age Ageing*. 2010;39:603–609.

29. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: The impact of frailty. *Arch Intern Med*. 2012;172:1162–1168.

30. Benetos A, Labat C, Rossignol P, et al. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: The PARTAGE study. *JAMA Intern Med*. 2015;175:989–995.

31. Conway KS, Forbang N, Beben T, Criqui MH, Ix JH, Rifkin DE. Relationship between 24-hour ambulatory blood pressure and cognitive function in community-living older adults: The UCSD ambulatory blood pressure study. *Am J Hypertens*. 2015;pii:hpv042. [Epub ahead of print]

32. Luukinen H, Airaksinen KE. Orthostatic hypotension predicts vascular death in older diabetic patients. *Diabetes Res Clin Pract*. 2005;67:163–166.

33. Hiitola P, Enlund H, Kettunen R, Sulkava R, Hartikainen S. Postural changes in blood pressure and the prevalence of orthostatic hypotension among home-dwelling elderly aged 75 years or older. *J Hum Hypertens*. 2009;23:33–39.

34. Wright JT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: The minority view. *Ann Intern Med*. 2014;160:499–503.