Kidney Function and Estimated Vascular Risk in Patients with Primary Dyslipidemia

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Abstract: Background: Chronic kidney disease (CKD) is associated with increased vascular risk. Some studies suggested that considering markers of CKD might improve the predictive accuracy of the Framingham risk equation.

Aim: To evaluate the links between kidney function and risk stratification in patients with primary dyslipidemia.

Methods: Dyslipidemic patients (n = 156; 83 men) who were non-smokers, did not have diabetes mellitus or evident vascular disease and were not on lipid-lowering or antihypertensive agents were recruited. Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault equation. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation. We estimated vascular risk using the Framingham equation.

Results: In both men and women, there was a significant negative correlation between estimated Framingham risk and both eGFR and CrCl (p < 0.001 for all correlations). When men were divided according to creatinine tertiles, there were no significant differences in any parameter between groups. When men were divided according to either eGFR or CrCl tertiles, all estimated Framingham risks significantly increased as renal function declined (p<0.001 for all trends). When women were divided according to creatinine tertiles, all estimated Framingham risks except for stroke significantly increased as creatinine levels increased. When women were divided according to either eGFR or CrCl tertiles, all estimated Framingham risks significantly increased as renal function declined.

Conclusions: Estimated vascular risk increases as renal function declines. The possibility that incorporating kidney function in the Framingham equation will improve risk stratification requires further evaluation.

Key Words: Creatinine, estimated glomerular filtration rate, chronic kidney disease, vascular risk, Framingham risk score.

INTRODUCTION

Primary prevention of vascular disease should be guided by the assessment of global risk [1-3]. Patients with higher vascular risk should be managed more aggressively [1, 3, 4]. A number of risk estimation engines that consider different risk factors have been developed [5, 6]. The Framingham risk score for subjects without evident vascular disease is well established [5].

The Framingham calculation considers the following vascular risk factors: age, gender, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), smoking, systolic blood pressure (SBP), diastolic blood pressure (DBP), the presence of diabetes mellitus (DM) and left ventricular hypertrophy [5]. Limitations of the Framingham risk equation include the absence of family history (FaHist) of premature vascular disease and age limits [1, 7, 8]. Furthermore, triglyceride (TG) levels and potentially relevant emerging risk factors are not considered [1, 7, 8]. In some studies, the assessment of emerging risk factors, such as high sensitivity C-reactive protein (hsCRP), added to the prognostic accuracy of the Framingham risk equation [9,10]. Similarly, chronic kidney disease (CKD) is associated with increased vascular risk in the general population [11-14]. Some studies suggested that considering markers of CKD might improve the predictive accuracy of the Framingham equation [15-17].

The aim of the present study was to evaluate the links between kidney function and risk stratification (using the Framingham equation) in non-smokers with primary dyslipidemia and no evident vascular disease or DM.
METHODS

Patient Selection

The records of 645 consecutive patients referred to a specialist centre for dyslipidemia were assessed [18, 19]. Among these patients, 234 untreated 
1. Treatment with any lipid lowering or antihypertensive agent during the previous 4 months.
2. Those with fasting serum glucose concentration > 5.0 mmol/l required a normal oral glucose tolerance test in order to be included in the survey.
3. Abnormal liver function tests: Reference ranges were: aspartate aminotransferase = 5 - 40 u/l; alanine aminotransferase = 5 - 40 u/l; gamma-glutamyl transferase = 10 - 48 u/l; alkaline phosphatase = 35 - 130 u/l; albumin = 35 - 55 g/l; bilirubin = 3 - 17 μmol/l (values up to 25 μmol/l were allowed provided all other liver function tests were normal).
4. Abnormal renal function: Reference ranges were: urea = 3.0 - 6.5 mmol/l (values up to 7.5 mmol/l were allowed for those above the age of 70 years); creatinine = 60 - 120 μmol/l; sodium = 135 - 145 mmol/l; potassium = 3.5 - 5.0 mmol/l.
5. Abnormal thyroid function tests: Reference ranges were: thyroid stimulating hormone = 0.5 - 4.7 mU/l; free thyroxine = 10 - 25 pmol/l.
6. Declared or determined history of alcohol or drug abuse. For alcohol consumption, the limits were set at 21 and 14 units/week for men and women, respectively.
7. Psychiatric conditions, whether involving medication or not.
8. Chronic inflammatory disease (e.g. rheumatoid arthritis, Crohn’s disease, ulcerative colitis, collagen diseases) or cancer [since an acute phase response may influence several variables (e.g. HDL-C)] [20-23].
9. Treatment with retinoic acid derivatives, tamoxifen, androgens, oestrogens (hormone replacement therapy or oral contraceptives), progestins, fish oils or ciclosporin since these drugs may exert effects on lipids [24-28].
10. Current or recent (4-month) pregnancy.
11. Current smokers or those who quit had quit for less than 6 months before sampling. A 6-month period was selected to allow time for reversal of measured variables within a practical time frame.

Clinical and Laboratory Investigations

Collection of samples: All samples were collected in the morning after fasting for a minimum of 12 h with water only allowed.

Lipid profile: Serum TC, HDL-C and TG levels were assayed by standard enzymatic methods (Boehringer Mannheim, Sussex, England) adapted for the Hitachi 911 analyser (HDL-C was measured after precipitating apolipoprotein B using a phosphotungstate procedure). Serum low density lipoprotein cholesterol (LDL-C) levels were calculated by the Friedewald formula. Patients with serum TG levels > 4.5 mmol/l, in whom LDL-C cannot be determined by the above formula, are not included in the analysis.

Liver and renal function profiles and serum glucose concentration were all determined by standard methods used in our department.

Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault equation: CrCl (ml/min) = [140 – age (in years)] x [weight (in kg)] x 0.85 (if female) / [72 x serum creatinine (in mg/dl)] [29]. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation: eGFR (ml/min/1.73 m²) = 186 x [serum creatinine (in mg/dl)]^1.154 x [age (in years)] ^(-0.203) x 0.742 (if female) x 1.210 (if black) [30].

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Calculation of Vascular Risk Using the Framingham Equation [www.bhsoc.org]

The Framingham risk engine can only be used to calculate vascular risk in the absence of cardiovascular disease (CVD). The following variables are considered: age, gender, SBP and DBP, serum TC and HDL-C levels, smoking status and the presence/absence of DM or left ventricular hypertrophy based on electrocardiographic criteria [5]. The equation estimates the 10-year risk for coronary heart disease (CHD), stroke and overall CVD based on either SBP (SBP-CHD, SBP-stroke and SBP-CVD, respectively) or DBP (DBP-CHD, DBP-stroke and DBP-CVD, respectively). We also estimated CVD risk taking a FaHist of premature vascular disease (any event before the age of 60 years) into consideration (termed SBP-CVD+FaHist and DBP-CVD+FaHist, respectively). A positive FaHist was considered to add 50% to the overall risk.

The Framingham equation has age limits (32 to 74 years). To increase the number of patients, men aged 24-31 years were entered as 32 years old and those aged 75-76 years were entered as 74 years old. Similarly, women aged 27-31 years were entered as 32 and those aged 75-78 years were entered as 74 years old.

Statistical Analysis

All data were analyzed using the statistical package SPSS (version 12.0; SPSS Inc., Chicago, IL). Continuous values are expressed as median and range. Correlations between variables were assessed using Spearman Rank correlation. The Kruskal-Wallis test was used to assess the trend of variables divided according to creatinine, eGFR or CrCl tertiles. The chi-square test was used to compare the agreement between eGFR and CrCl in classifying patients in tertiles of renal function. Because we assessed the correlation between indices of renal function (creatinine, eGFR and CrCl) and 22 other parameters, a 2-tailed p < 0.031 was considered significant [31]. In all other analyses, a 2-tailed p < 0.05 was considered significant.
RESULTS

The clinical characteristics of the 156 patients (83 men) enrolled in this survey are listed in Table 1. Estimated risk for CHD, stroke and CVD based on SBP and DBP are shown in Table 2.

Significant correlations between the indices of renal function (creatinine, eGFR and CrCl) and other parameters are shown in Tables 3 and 4. In men, there was a significant positive correlation between creatinine levels and SBP-CHD, SBP-CVD, DBP-CHD and DBP-CVD (Table 3). In women, creatinine levels correlated significantly with all estimated risks (Table 4). In both men and women, there was a significant negative correlation between all estimated risks and both eGFR and CrCl (p < 0.001 for all correlations; Tables 3 and 4).

When men were divided according to creatinine tertiles, there were no differences in any parameter between groups. When men were divided according to either eGFR or CrCl tertiles, all estimated risks increased significantly as renal

Table 1. Clinical Characteristics of the Study Population

|                | Men (n = 83) | Women (n = 73) |
|----------------|-------------|---------------|
| Age (years)    | 49 (24-76)  | 55 (27-78)    |
| Weight (kg)    | 81.2 (61.1-119.0) | 65.3 (45.7-96.0) |
| Systolic blood pressure (mmHg) | 130 (85-170) | 135 (100-185) |
| Diastolic blood pressure (mmHg) | 80 (60-100) | 80 (70-115) |
| Lipid profile  |             |               |
| TC (mmol/l)    | 7.1 (4.5-12.2) | 7.6 (4.5-11.7) |
| LDL-C (mmol/l) | 5.0 (2.4-9.3) | 5.4 (2.7-9.7) |
| HDL-C (mmol/l) | (0.6-2.1) | 1.4 (0.6-2.6) |
| TG (mmol/l)    | 2.2 (0.7-7.4) | 1.6 (0.5-4.8) |
| TC/HDL-C       | 6.3 (3.6-14.2) | 5.6 (2.7-12.3) |
| LDL-C/HDL-C    | 4.3 (2.4-10.2) | 4.0 (1.4-8.9) |
| Lipoprotein a (g/l) | 0.25 (0.05-2.10) | 0.34 (0.05-1.54) |
| Fibrinogen (g/l) | 3.05 (1.44-5.47) | 3.51 (2.11-6.29) |
| Glucose (mmol/l) | 4.8 (3.6-5.6) | 4.7 (3.3-6.1) |
| Urate (mmol/l) | 0.38 (0.21-0.81) | 0.28 (0.17-0.51) |
| Renal function |             |               |
| Creatinine (μmol/l) | 93 (72-112) | 74 (51-120) |
| eGFR (MDRD) (ml/min/1.73 m²) | 80 (62-115) | 76 (42-120) |
| Creatinine clearance (CG) (ml/min) | 101 (58-153) | 82 (30-148) |

TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease equation. CG, cockcroft-gault equation.

Table 2. Estimated Vascular Risk of the Study Population

|               | Men (n = 83) | Women (n = 73) |
|---------------|-------------|---------------|
| SBP-CHD       | 11.2 (0.7-41.4) | 9.1 (0.0-22.1) |
| SBP-stroke    | 1.1 (0.1-8.5) | 1.4 (0.1-9.7) |
| SBP-CVD       | 12.4 (0.8-49.3) | 10.6 (0.1-31.8) |
| DBP-CHD       | 10.7 (0.5-40.0) | 9.3 (0.0-23.1) |
| DBP-stroke    | 0.9 (0.0-8.7) | 1.3 (0.0-8.3) |
| DBP-CVD       | 11.7 (0.5-45.4) | 11.0 (0.0-31.4) |
| SBP-CVD + FaHist | 14.6 (1.2-73.9) | 12.0 (0.1-47.7) |
| DBP-CVD + FaHist | 14.3 (0.7-68.1) | 13.5 (0.0-47.1) |

CHD, coronary heart disease; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FaHist, family history; SBP-CHD, estimated CHD risk based on SBP; SBP-stroke, estimated stroke risk based on SBP; SBP-CVD, estimated CVD risk based on SBP; DBP-CHD, estimated CHD risk based on DBP; DBP-stroke, estimated stroke risk based on DBP; DBP-CVD, estimated CVD risk based on DBP; SBP-CVD + FaHist, estimated CVD risk based on SBP and the presence of FaHist; DBP-CVD + FaHist, estimated CVD risk based on DBP and the presence of FaHist.
function declined (p<0.001 for all trends; Tables 5 and 6). It should be noted that there was significant disagreement in the classification of men in tertiles according to eGFR or CrCl. Thus, among men in the lowest, middle and higher eGFR tertile, only 46, 29 and 70%, respectively, were also in the lowest, middle and higher CrCl tertile, respectively (p<0.001).

When women were divided according to creatinine tertiles, all estimated risks except for stroke significantly increased as creatinine levels increased (Table 7). When women were divided according to either eGFR or CrCl tertiles, all estimated risks significantly increased as renal function declined (Tables 8 and 9). There was significant disagreement in the classification of women in tertiles

Table 3. Significant Correlations Between Markers of Renal Function and Other Parameters in Men (n = 83). Due to Multiple Correlations, a p value < 0.031 is Considered Significant

| Correlations between serum creatinine levels and other parameters | Parameter | r     | P       |
|---------------------------------------------------------------|----------|-------|---------|
|                                                              | TC       | 0.252 | 0.022   |
|                                                              | LDL-C    | 0.249 | 0.023   |
|                                                              | TC/HDL-C | 0.256 | 0.02     |
|                                                              | LDL-C/HDL-C | 0.291 | 0.008 |
|                                                              | SBP-CHD  | 0.289 | 0.008   |
|                                                              | SBP-CVD  | 0.259 | 0.018   |
|                                                              | DBP-CHD  | 0.292 | 0.007   |
|                                                              | DBP-CVD  | 0.268 | 0.014   |

| Correlations between eGFR (MDRD) and other parameters | Parameter | r     | P       |
|------------------------------------------------------|----------|-------|---------|
|                                                      | Age      | -0.544 | <0.001   |
|                                                      | SBP-CHD  | -0.605 | <0.001   |
|                                                      | SBP-stroke | -0.456 | <0.001 |
|                                                      | SBP-CVD  | -0.588 | <0.001   |
|                                                      | DBP-CHD  | -0.620 | <0.001   |
|                                                      | DBP-stroke | -0.520 | <0.001 |
|                                                      | DBP-CVD  | -0.607 | <0.001   |
|                                                      | SBP-CVD + FaHist | -0.501 | <0.001 |
|                                                      | DBP-CVD + FaHist | -0.533 | <0.001 |

| Correlations between creatinine clearance (CG) and other parameters | Parameter | r     | P       |
|---------------------------------------------------------------------|----------|-------|---------|
|                                                                     | Age      | -0.807 | <0.001   |
|                                                                     | Weight   | 0.599 | <0.001   |
|                                                                     | HDL-C    | -0.283 | 0.010     |
|                                                                     | SBP-CHD  | -0.697 | <0.001   |
|                                                                     | SBP-stroke | -0.703 | <0.001 |
|                                                                     | SBP-CVD  | -0.708 | <0.001   |
|                                                                     | DBP-CHD  | -0.714 | <0.001   |
|                                                                     | DBP-stroke | -0.763 | <0.001 |
|                                                                     | DBP-CVD  | -0.727 | <0.001   |
|                                                                     | SBP-CVD + FaHist | -0.632 | <0.001 |
|                                                                     | DBP-CVD + FaHist | -0.667 | <0.001 |

For abbreviations, see Tables 1 and 2.
Table 4. Significant Correlations Between Markers of Renal Function and Other Parameters in Women (n = 73). Due to Multiple Correlations, a p value < 0.031 is Considered Significant

| Correlations between serum creatinine levels and other parameters | Parameter | r   | p   |
|-------------------------------------------------------------------|----------|-----|-----|
|                                                                   | Age      | 0.330 | 0.004 |
|                                                                   | Triglycerides | 0.273 | 0.019 |
|                                                                   | Glucose  | 0.258 | 0.029 |
|                                                                   | Urate    | 0.408 | 0.001 |
|                                                                   | SBP-CHD  | 0.361 | 0.002 |
|                                                                   | SBP-stroke | 0.317 | 0.006 |
|                                                                   | SBP-CVD  | 0.349 | 0.002 |
|                                                                   | DBP-CHD  | 0.348 | 0.003 |
|                                                                   | DBP-stroke | 0.344 | 0.003 |
|                                                                   | DBP-CVD  | 0.348 | 0.003 |
|                                                                   | SBP-CVD+ FaHist | 0.360 | 0.002 |
|                                                                   | DBP-CVD+ FaHist | 0.370 | 0.001 |

| Correlations between eGFR (MDRD) and other parameters | Parameter | r   | p   |
|------------------------------------------------------|----------|-----|-----|
|                                                     | Age      | -0.535 | <0.001 |
|                                                     | Fibrinogen | -0.298 | 0.011 |
|                                                     | Glucose  | -0.342 | 0.003 |
|                                                     | Triglycerides | -0.308 | 0.008 |
|                                                     | Urate    | -0.435 | <0.001 |
|                                                     | SBP-CHD  | -0.510 | <0.001 |
|                                                     | SBP-stroke | -0.502 | <0.001 |
|                                                     | SBP-CVD  | -0.511 | <0.001 |
|                                                     | DBP-CHD  | -0.499 | <0.001 |
|                                                     | DBP-stroke | -0.544 | <0.001 |
|                                                     | DBP-CVD  | -0.515 | <0.001 |
|                                                     | SBP-CVD+ FaHist | -0.525 | <0.001 |
|                                                     | DBP-CVD+ FaHist | -0.538 | <0.001 |

| Correlations between creatinine clearance (CG) and other parameters | Parameter | r   | p   |
|---------------------------------------------------------------------|----------|-----|-----|
|                                                                     | Age      | -0.685 | <0.001 |
|                                                                     | Weight   | 0.318 | 0.006 |
|                                                                     | Fibrinogen | -0.275 | 0.019 |
|                                                                     | Glucose  | -0.303 | 0.01  |
|                                                                     | SBP-CHD  | -0.556 | <0.001 |
|                                                                     | SBP-stroke | -0.628 | <0.001 |
|                                                                     | SBP-CVD  | -0.582 | <0.001 |
|                                                                     | DBP-CHD  | -0.531 | <0.001 |
|                                                                     | DBP-stroke | -0.649 | <0.001 |
### Table 4 contd....

| Correlations between creatinine clearance (CG) and other parameters | r    | p      |
|-------------------------------------------------------------------|------|--------|
| DBP-CVD                                                           | -0.569 | <0.001 |
| SBP-CVD+ FaHist                                                   | -0.607 | <0.001 |
| DBP-CVD+ FaHist                                                   | -0.612 | <0.001 |

For abbreviations, see Table 2.

### Table 5. Significant Differences Between Groups when men were Divided According to Estimated Glomerular Filtration Rate Tertiles (Modification of Diet in Renal Disease Equation)

| Estimated Glomerular Filtration Rate Tertiles (ml/min/1.73 m^2) | p for Trend |
|-----------------------------------------------------------------|-------------|
| < 75 (n = 28)                                                   | 75-86 (n = 28) | > 86 (n = 27) |
| LDL-C (mmol/l)                                                  | 5.2 (3.3-7.7) | 4.5 (2.4-6.9) | 4.9 (2.6-9.3) | 0.028 |
| TC/HDL-C                                                        | 7.2 (4.6-10.9) | 5.5 (3.6-9.0) | 6.4 (4.6-14.2) | 0.002 |
| LDL-C/HDL-C                                                     | 5.2 (3.1-7.7) | 3.5 (2.4-6.5) | 4.3 (2.8-10.2) | <0.001 |
| Age (years)                                                     | 52.5 (43-76) | 51.5 (25-67) | 36 (24-70) | <0.001 |
| SBP-CHD                                                         | 17.2 (6.9-41.4) | 10.2 (1.3-22.8) | 5.4 (0.7-25.9) | <0.001 |
| SBP-stroke                                                      | 1.5 (0.2-8.5) | 1.3 (0.1-4.4) | 0.4 (0.1-7.7) | <0.001 |
| SBP-CVD                                                         | 18.2 (7.1-49.3) | 11.6 (1.4-26.0) | 5.7 (0.8-32.5) | <0.001 |
| DBP-CHD                                                         | 16.3 (7.7-40.0) | 10.0 (0.7-22.8) | 5.0 (0.5-24.6) | <0.001 |
| DBP-stroke                                                      | 1.2 (0.4-8.7) | 1.2 (0.0-3.9) | 0.2 (0.0-4.7) | <0.001 |
| DBP-CVD                                                         | 17.8 (8.5-45.4) | 10.8 (0.7-25.8) | 5.2 (0.5-29.3) | <0.001 |
| SBP-CVD+ FaHist                                                 | 19.8 (7.1-73.9) | 14.6 (2.1-35.5) | 7.9 (1.2-32.5) | <0.001 |
| DBP-CVD+ FaHist                                                 | 19.2 (8.8-68.1) | 15.4 (1.0-32.8) | 7.3 (0.7-29.3) | <0.001 |

For abbreviations, see Tables 1 and 2.

### Table 6. Significant Differences Between Groups when men were Divided According to Creatinine Clearance (Cockcroft-Gault Equation)

| Creatinine Clearance Tertiles (ml/min) | p for Trend |
|---------------------------------------|-------------|
| < 90 (n = 28)                         | 90-109 (n = 28) | > 109 (n = 27) |
| TG (mmol/l)                           | 1.6 (0.7-3.3) | 2.5 (0.8-7.4) | 2.5 (0.9-4.8) | 0.02 |
| HDL-C (mmol/l)                        | 1.2 (0.7-2.1) | 1.1 (0.8-1.9) | 1.0 (0.6-1.4) | 0.042 |
| Weight (kg)                           | 72.9 (61.1-83.0) | 87.1 (62.0-96.6) | 84.5 (72.2-119.0) | <0.001 |
| Age (years)                           | 58.5 (44-76) | 49 (31-64) | 34 (24-51) | <0.001 |
| SBP-CHD                               | 16.1 (7.9-41.4) | 12.1 (1.6-24.8) | 5.2 (0.7-13.2) | <0.001 |
| SBP-stroke                            | 2.2 (0.5-8.5) | 1.1 (0.2-7.7) | 0.3 (0.1-1.5) | <0.001 |
| SBP-CVD                               | 18.4 (8.4-49.3) | 13.4 (2.8-32.5) | 5.6 (0.8-14.6) | <0.001 |
| DBP-CHD                               | 16.5 (7.2-40.0) | 12.3 (1.2-21.2) | 5.0 (0.5-12.9) | <0.001 |
| DBP-stroke                            | 2.3 (0.5-8.7) | 0.9 (0.1-4.2) | 0.2 (0.0-1.2) | <0.001 |
| DBP-CVD                               | 18.3 (8.5-45.4) | 13.6 (1.3-25.2) | 5.2 (0.5-13.8) | <0.001 |
| SBP-CVD+FaHist                        | 19.4 (10.8-73.9) | 16.7 (4.2-36.9) | 7.6 (1.2-20.7) | <0.001 |
| DBP-CVD+FaHist                        | 19.7 (8.5-68.1) | 16.3 (1.9-33.3) | 6.4 (0.7-17.8) | <0.001 |

For abbreviations, see Tables 1 and 2.
Table 7. Significant Differences Between Groups when Women were Divided According to Serum Creatinine Tertiles

| Parameter          | Serum Creatinine Tertiles (μmol/l) | P for Trend |
|--------------------|------------------------------------|-------------|
|                    | ≤ 67 (n = 24)                      | 68-79 (n = 24) | ≥ 80 (n = 25) |
| **DBP (mmHg)**     | 80 (70-115)                        | 85 (70-110)   | 80 (70-105)   | 0.041 |
| **TC (mmol/l)**    | 7.6 (4.9-10.1)                     | 7.1 (4.5-11.7) | 8.0 (6.0-10.1) | 0.023 |
| **TG (mmol/l)**    | 1.2 (0.5-3.6)                      | 1.7 (0.6-4.8) | 1.8 (0.6-3.7) | 0.044 |
| **LDL-C (mmol/l)** | 5.7 (2.7-8.4)                      | 4.6 (2.7-9.7) | 5.9 (3.9-7.8) | 0.028 |
| **Urate (mmol/l)** | 0.24 (0.17-0.33)                   | 0.30 (0.21-0.50) | 0.32 (0.19-0.51) | 0.006 |
| **SBP-CHD**        | 4.8 (0.2-22.1)                     | 6.4 (0.0-18.3) | 11.2 (1.0-20.8) | 0.015 |
| **SBP-CVD**        | 6.3 (0.3-31.8)                     | 9.2 (0.1-24.8) | 13.3 (1.4-24.1) | 0.03 |
| **DBP-CHD**        | 4.9 (0.1-23.1)                     | 8.6 (0.0-22.4) | 12.3 (0.9-22.8) | 0.022 |
| **DBP-CVD**        | 6.3 (0.1-31.4)                     | 10.3 (0.0-24.2) | 14.2 (1.2-25.8) | 0.029 |
| **SBP-CVD+FaHist** | 8.1 (0.3-47.7)                     | 9.6 (0.1-24.8) | 18.3 (2.1-36.1) | 0.013 |
| **DBP-CVD+FaHist** | 8.0 (0.1-47.1)                     | 11.0 (0.0-26.4) | 18.3 (1.8-27.0) | 0.009 |

For abbreviations, see Tables 1 and 2.

Table 8. Significant Differences Between Groups when Women were Divided According to Estimated Glomerular Filtration Rate Tertiles (Modification of Diet in Renal Disease Equation)

| Estimated Glomerular Filtration Rate Tertiles (ml/min/1.73 m²) | P for Trend |
|---------------------------------------------------------------|-------------|
| < 69 (n = 24)                                                 | 69-83 (n = 25) | > 83 (n = 24) |
| **DBP (mmHg)**                                               | 82 (70-105)   | 85 (70-115)   | 80 (70-90)   | 0.005 |
| **TG (mmol/l)**                                              | 1.9 (0.9-3.7) | 1.7 (0.6-4.8) | 1.2 (0.5-3.6) | 0.012 |
| **Fibrinogen (g/l)**                                         | 3.64 (2.54-5.76) | 3.58 (2.32-5.16) | 3.15 (2.11-6.29) | 0.028 |
| **Glucose (mmol/l)**                                         | 4.8 (4.2-5.6) | 4.7 (3.7-6.1) | 4.4 (3.3-6.0) | 0.032 |
| **Urate (mmol/l)**                                           | 0.32 (0.19-0.51) | 0.30 (0.21-0.50) | 0.25 (0.17-0.33) | 0.001 |
| **Age (years)**                                              | 61 (40-72)    | 55 (38-78)    | 48 (27-67)    | <0.001 |
| **SBP-CHD**                                                  | 12.1 (1.0-20.8) | 8.6 (1.1-22.1) | 3.6 (0.0-18.5) | <0.001 |
| **SBP-stroke**                                               | 2.2 (0.4-7.8) | 1.5 (0.2-9.7) | 0.5 (0.1-6.3) | 0.001 |
| **SBP-CVD**                                                  | 14.7 (1.4-24.1) | 10.0 (1.3-31.8) | 4.6 (0.1-19.5) | <0.001 |
| **DBP-CHD**                                                  | 12.5 (0.9-22.8) | 9.8 (1.2-23.1) | 3.4 (0.0-19.2) | <0.001 |
| **DBP-stroke**                                               | 2.0 (0.3-5.1) | 1.6 (0.2-8.3) | 0.6 (0.0-2.9) | <0.001 |
| **DBP-CVD**                                                  | 14.8 (1.2-25.8) | 11.4 (1.4-31.4) | 4.1 (0.0-20.0) | <0.001 |
| **SBP-CVD+FaHist**                                          | 20.2 (2.1-36.1) | 10.8 (1.9-47.7) | 5.2 (0.1-25.6) | <0.001 |
| **DBP-CVD+FaHist**                                          | 18.4 (1.8-27.0) | 12.8 (1.9-47.1) | 4.1 (0.0-24.0) | <0.001 |

For abbreviations, see Tables 1 and 2.

according to eGFR or CrCl. Thus, among women in the lowest, middle and higher eGFR tertile, only 71, 44 and 67%, respectively, were also in the lowest, middle and higher CrCl tertile, respectively (p < 0.001).

**DISCUSSION**

CKD is defined as the presence of either eGFR < 60 ml/min/1.73m² or persistent albuminuria [30]. The prevalence of CKD is rising due to the progressive aging of the
population and the increasing number of patients with type 2 DM [32-36]. It was reported that approximately 13.1% of the US adult population has CKD [37]. The prevalence of CKD in the UK ranges between 5.8 and 12.0% [38,39]. In both countries, CKD is more frequent in women than in men [37, 39].

Several studies showed that impaired renal function is associated with increased vascular mortality in the general population [11-14], in patients with stable CHD [40-42], acute coronary syndromes (ACS) [43, 44], stroke [45] or peripheral arterial disease (PAD) [46]. CKD is also a risk factor for stroke in the general population [47] and in patients with CHD [48] although others reported an association only with hemorrhagic stroke [49]. CKD is associated with increased risk for PAD [50] and renal artery stenosis in the general population [51] and correlates with ankle-brachial index (ABI) in patients with PAD [52]. Both established and emerging risk factors are implicated in the increased vascular morbidity and mortality in CKD [53].

In our study, estimated vascular risk significantly increased as kidney function deteriorated. In previous reports, the Framingham risk score was higher in patients with CKD than in those with normal kidney function [54]. In addition, the Framingham model appears to underestimate vascular risk in patients with CKD [55]. In contrast, an analysis of the Atherosclerosis Risk in the Communities (ARIC) study showed that accounting for CKD did not improve discrimination of the Framingham equation for vascular events [17]. In the same study, considering renal function improved discrimination for total mortality in white men but not in white women [17].

The MDRD equation is the proposed method for eGFR assessment in clinical practice [30]. It is currently recommended that serum creatinine levels should not be used as the sole means to assess kidney function [33]. However, the MDRD equation was developed in patients with CKD and appears to be less accurate in patients with normal kidney function or moderately reduced eGFR [30,56,57]. The Cockcroft-Gault equation also misclassified approximately 30% of subjects in population studies [58]. Significant differences in classification regarding renal function comparing MDRD and Cockcroft-Gault equations were also seen in the present study. Other indices of kidney function might also be useful. Cystatin C levels might reflect GFR more accurately than creatinine [59]. Elevated cystatin C levels were associated with vascular events in elderly subjects [60] and in patients with established CHD [61]. However, cystatin C levels also show variations depending on age, gender, body weight, smoking and presence of inflammation [62].

We estimated vascular risk using the Framingham risk equation. Some studies performed in the UK showed that the Framingham engine accurately predicts vascular events [63] although others reported an overestimation of CHD risk with this model [64-66]. A meta-analysis showed a considerable variation in the predictive value of the Framingham risk score in different populations [67]. It appears to overestimate risk in low risk populations and to underestimate risk in high risk populations [67]. The Prospective Cardiovascular Munster (PROCAM) score is also used to estimate vascular risk [6]. This score considers all risk factors of the Framingham equation but replaces LDL-C for TC levels and includes TG levels and FaHist of CHD [6]. Elevated TG levels appear to be associated with increased vascular risk [68]. Studies in the UK showed that PROCAM and Framingham models have similar predictive values [65, 66]. In contrast, we reported that, in dyslipidemic patients without established vascular

| Table 9. Significant Differences Between Groups when Women where Divided According to Creatinine Clearance Tertiles (Cockcroft-Gault Equation) |
|---------------------------------------------------------------|
| Creatinine Clearance Tertiles (ml/min) | < 72 (n = 24) | 72-89 (n = 25) | > 90 (n = 24) | p for Trend |
|---------------------------------------------------------------|
| Fibrinogen (g/l) | 395 (234-576) | 348 (227-629) | 335 (211-446) | 0.039 |
| Glucose (mmol/l) | 4.7 (3.9-6.1) | 4.8 (3.7-6.0) | 4.4 (3.3-5.6) | 0.024 |
| Weight (kg) | 61.9 (45.7-79.6) | 66.9 (46.3-84.8) | 68.7 (53.6-96.0) | 0.027 |
| Age (years) | 65 (40-78) | 54 (38-68) | 43 (27-71) | <0.001 |
| SBP-CHD | 11.8 (1.0-20.8) | 9.2 (1.1-22.1) | 3.8 (0.0-18.5) | <0.001 |
| SBP-stroke | 2.5 (0.4-8.7) | 1.2 (0.2-9.7) | 0.4 (0.1-3.5) | 0.001 |
| SBP-CVD | 15.1 (1.4-24.8) | 10.6 (1.3-31.8) | 4.6 (0.1-19.5) | <0.001 |
| DBP-CHD | 12.2 (0.9-22.8) | 9.4 (1.2-23.1) | 3.8 (0.0-19.2) | 0.001 |
| DBP-stroke | 2.9 (0.3-6.1) | 1.2 (0.2-8.3) | 0.4 (0.0-7.2) | <0.001 |
| DBP-CVD | 16.7 (1.2-25.8) | 11.4 (1.4-31.4) | 4.4 (0.0-20.0) | <0.001 |
| SBP-CVD+ FaHist | 19.1 (2.1-36.1) | 12.9 (1.9-47.7) | 4.9 (0.1-25.6) | <0.001 |
| DBP-CVD+ FaHist | 18.4 (1.8-27.0) | 14.3 (1.9-47.1) | 4.5 (0.0-24.0) | <0.001 |

For abbreviations, see Tables 1 and 2.
Kidney Function and Estimated Vascular Risk

function declines. The possibility that incorporating kidney function in the Framingham predictive equation will improve risk stratification requires further work.

ABBREVIATIONS

ABI = Ankle-brachial index
ACS = Acute coronary syndromes
ARIC = Atherosclerosis risk in the communities
CHD = Coronary heart disease
CKD = Chronic kidney disease
CrCl = Creatinine clearance
CVD = Cardiovascular disease
DBP = Diastolic blood pressure
DM = Diabetes mellitus
eGFR = Estimated glomerular filtration rate
FaHist = Family history
HDL-C = High density lipoprotein cholesterol
hsCRP = High sensitivity C-reactive protein
LDL-C = Low density lipoprotein cholesterol
MDRD = Modification of diet in renal disease
PAD = Peripheral arterial disease
PROCAM = Prospective cardiovascular munster
SBP = Systolic blood pressure
SHARP = Study of heart and renal protection
TC = Total cholesterol
VA-HIT = Veterans’ affairs high-density lipoprotein intervention trial

DECLARATION OF INTEREST

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