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.

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METHODS

Patient Selection

The records of 645 consecutive patients referred to a specialist centre for dyslipidemia were assessed [18, 19]. Among these patients, we identified 234 patients (144 men) without overt vascular disease or DM. In order to create an even more homogeneous patient group, the following exclusion criteria were also applied [18, 19]:

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 m^2) = 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].

The Department of Clinical Biochemistry, Royal Free Hospital participates in several quality assurance programs and has full Clinical Pathology Accreditation (CPA).

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 m^2)	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.

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 ratio	0.256	0.02
LDL-C/HDL-C ratio	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**.

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 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		
Parameter	**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 where 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 where 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 where 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 where 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
	< 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/1.73m^2 or persistent albuminuria [30]. The prevalence of CKD is rising due to the progressive aging of the

Table 9. Significant Differences Between Groups when Women where Divided According to Creatinine Clearance Tertiles (Cockcroft-Gault Equation)

	Creatinine Clearance Tertiles (ml/min)			p for Trend
	< 72 (n = 24)	72-89 (n = 25)	> 90 (n = 24)	
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**.

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

disease, the Framingham risk score predicted higher risk than PROCAM [69]. We did not use the PROCAM calculation in this study due to its narrow age limits [6].

It is of interest that statins appear to prevent the decline of renal function in high risk patients without established vascular disease and in patients with CVD [40, 41, 70-78]. A number of small studies also reported that statins might reduce albuminuria [79, 80]. Other lipid profile modifying agents, including ezetimibe and omega-3 fatty acids, might also "protect" kidney function [81-86]. In contrast, fibrates appear to raise serum creatinine levels [87-94]. It was suggested that the fibrates-induced rise in creatinine level is due to increased production of creatinine and does not reflect a true decline of kidney function [91, 93, 95]. In addition, fibrates appear to reduce microalbuminuria in diabetic patients [96, 97].

Subgroup analyses of randomized controlled trials in high risk patients without established vascular disease and in patients with CHD showed that statins reduce vascular risk in patients with CKD [42, 98-101]. The ongoing Study of Heart and Renal Protection (SHARP) will assess the effects of the simvastatin plus ezetimibe combination treatment in patients with CKD but without established CHD [102]. In the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), gemfibrozil reduced vascular events in patients with CKD and established CHD [103]. However, there was an increased risk of sustained increase in creatinine levels in the gemfibrozil group [103].

Uric acid levels have not been consistent predictors of vascular risk [40,104,105]. Some evidence identified a relationship only in women [105]. Therefore it is of interest that in the present study uric acid levels showed a significant trend in relation to serum creatinine levels and eGFR only in women.

A limitation of our study is that we did not evaluate the presence of albuminuria, another diagnostic criterion for CKD [30] that is also associated with increased vascular risk [106-108]. Evaluation of both eGFR and albuminuria is currently recommended for the detection of CKD [30] since patients with CKD might only have a low eGFR or isolated albuminuria [109-111]. In addition, albuminuria and eGFR appear to predict vascular disease independently of each other [110]. Albuminuria predicted vascular events in hypertensive patients independently of the Framingham risk score [112]. It also appears that considering albuminuria might improve the predictive accuracy of the Framingham risk equation [15,16]. However, the Framingham Heart study reported that only reduced eGFR predicted all cause mortality whereas microalbuminuria did not [111]. A "statistical" disadvantage is that many of the variables that differed between the tertiles of renal function are actually included (directly or indirectly) in the Framingham equation.

An advantage of our study is the homogeneous nature of the population. None of the participants had DM or overt CVD, none were smokers and they were not taking any lipid lowering or antihypertensive drugs.

In conclusion, estimated vascular risk (using the Framingham equation) progressively increases as renal 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

This study was performed independently; no company or institution supported it financially. Some of the authors have attended conferences, given lectures and participated in advisory boards or trials sponsored by various pharmaceutical companies. Konstantinos Tziomalos is supported by a grant from the Hellenic Atherosclerosis Society.

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