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Proteinuria and its associated factors in patients attending family medicine clinics in Dammam, Saudi Arabia

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Abstract:

BACKGROUND: Urinalysis is a simple, valuable, and low-cost tool for the detection of proteinuria, a significant risk factor for renal and cardiovascular diseases. The purpose of this study was to determine the rate of proteinuria and its associated risk factors in patients attending Family Medicine Clinics in Dammam, Saudi Arabia, as no study of that nature had previously been conducted.

MATERIALS AND METHODS: In this register-based cross-sectional study, data including urinary protein and other urinalysis components ordered between January 2018 and January 2020 were collected from electronic medical records. In addition, data regarding nationality, gender, age, blood pressure, body mass index, serum human chorionic gonadotropin, fasting glucose, hemoglobin A1c (HbA1c), 25-hydroxy Vitamin D level, blood urea nitrogen (BUN), uric acid, creatinine, estimated glomerular filtration rate (eGFR), and lipid profile was also obtained. Proteinuria was classified as negative if no or trace protein was present, and positive if protein was ≥1+, and was considered overt proteinuria.

RESULTS: In total, results of 2942 urinalysis tests were included. The mean age of the patients was 42.4 ± 14.5 years; majority of the patients were females (62.3%) and were Saudis (68.8%). The rate of proteinuria was 4.2%. Saudi nationality, female gender, age ≥ 40 years, high systolic blood pressure, high diastolic blood pressure, fasting glucose ≥126, HbA1c ≥6.5%, BUN >20 mg/dl, creatinine >1.3 mg/dl, low eGFR <60, and high low-density lipoproteins cholesterol were significantly associated with proteinuria based on bivariate analysis. Using a logistic regression model, a statistically significant association was observed between proteinuria and advancing age, the presence of urinary casts, elevated serum creatinine level, and Saudi nationality.

CONCLUSION: The only variables that were independently associated with proteinuria using the logistic regression were the presence of casts in the urine, Saudi nationality, high creatinine level, and older age. These variables should be borne in mind by treating physicians.

Keywords:

Proteinuria, Saudi Arabia, urinalysis

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Introduction

Proteinuria is commonly seen in family medicine practice,[1] with a prevalence of 8%–33% in the general population.[2] It alerts physicians to possible chronic kidney disease (CKD) in patients with chronic conditions usually seen in primary healthcare, such as diabetes mellitus and hypertension.[1] The prevalence of both conditions is positively correlated proteinuria levels,[3] and all increase with advanced age.[2,4] Proteinuria and estimated glomerular filtration rate (eGFR) are used for CKD staging, according to the Kidney Disease Improving Global Outcomes guidelines.[2,5,6] Some studies suggest screening for proteinuria in adults

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with risk factors such as diabetes mellitus, hypertension, CKD, obesity, and smoking.[2] National screening is recommended in Saudi Arabia for urinary abnormalities including proteinuria in children.[7]

Urinalysis specificity for detecting proteinuria is high (95.0%), but the positive predictive value is very low (22.2%).[8] <1.5% of renal disease patients have asymptomatic proteinuria.[9] Furthermore, some studies do not recommend screening for renal failure because of the low sensitivity of urinalysis (80%).[8] It is crucial to determine whether the proteinuria is transient or persistent.[9] Transient proteinuria is a temporary finding after dehydration, emotional stress, fever, and exercise.[9] Meanwhile, persistent proteinuria should be assessed with other means of measuring protein in the urine, such as 24-h excretion or the protein–creatinine ratio.[9] False-negative proteinuria can occur in acidic, diluted urine, and in the presence of nonalbumin protein. In contrast, alkaline-concentrated urine and hematuria can cause false-positive results.[2,9,10] Dehydration, urinary tract infection, hematuria, and recent exercise can also give false-positive results.[2]

The risk factors of proteinuria studied previously found a link between proteinuria and impaired fasting glucose, elevated blood pressure,[4] higher triglyceride levels, and lower high-density lipoprotein (HDL) cholesterol levels.[11,12] In addition, obesity[12] and uric acid levels[4] were found to be associated with proteinuria. Another study revealed that the risk of Type 2 diabetes mellitus increased with the severity of proteinuria.[13]

The objectives of this study were to estimate the prevalence of proteinuria and determine its associated factors in patients of family medicine clinics in Dammam, Saudi Arabia.

Materials and Methods

A register-based cross-sectional study was conducted in family medicine clinics in Dammam, Saudi Arabia. Data for all ordered urinalysis tests performed for patients between January 2018 and January 2020 were included in this study. Tests of adults of both genders (including pregnant females) and all nationalities were included. Tests of patients younger than 18 years were excluded. The minimum required sample size was calculated using Epi-Info (Atlanta, Georgia, US) to be 384 with a 95% confidence interval (CI) and a precision of 5%, and the assumed abnormal urinalysis percentage was 50%. Ethical approval was obtained from the Institutional Review Board vide Letter No. IRB-2020-01-093 dated 29/03/2019, with a waiver for written consent, as data were collected from patient medical records only, and no human subjects were directly involved in this study.

Data were obtained from E-Health Services and Information Technology and collected from electronic medical records. Variables collected from the urinalysis test results included proteinuria and other components (color, clarity, and presence of casts, crystals, and blood) together with the corresponding patient's demographic data, including nationality, gender, and age. Body mass index (BMI), blood pressure, and laboratory bloodwork, including serum human chorionic gonadotropin (hCG), fasting glucose, hemoglobin A1c (HbA1c), uric acid, and 25-hydroxy Vitamin D levels were also collected. In addition, renal function test results provided information on blood urea nitrogen (BUN), creatinine, and eGFR levels. Lipid profiles comprised low-density lipoproteins (LDL) cholesterol, HDL cholesterol, triglyceride, and total cholesterol levels.

A Quantimetrix DipandSpin Urinalysis dipstick and microscopic control were used in the laboratory. Proteinuria was categorized as negative if there was no or trace protein in the urine and as positive if the level was ≥1+, indicating overt proteinuria. Trace proteinuria, 1+, 2+, and 3+ corresponded to 15, 30, 100, and 500 mg/dl, respectively. The color of normal urine was yellow, pale yellow, or straw. Urine that was dark yellow, amber, orange, red, or brown was categorized as abnormal. Urine clarity was defined as normal if clear or slightly cloudy and abnormal if cloudy or turbid. Negative or trace amounts of ketones, glucose, epithelial cells, mucous threads, and bacteria were considered normal, while ≥1+ was considered abnormal. Negative results for bilirubin, urobilinogen, ascorbic acid, blood, nitrite, leukocytes, yeast cells, non-squamous epithelial cells, and trichomonas were defined as normal, while the presence of trace amounts or ≥1+ was defined as abnormal. The presence of three or more red blood cells (RBCs) per high-power field (HPF) in urine was defined as hematuria, while the presence of more than five white blood cells (WBCs) per HPF was defined as pyuria. The normal range of urine-specific gravity was between 1.005 and 1.030, and the normal urinary pH was between 5.5 and 6.0. Urinary casts were considered normal if ≤1 were hyaline, granular, or hyaline granular and as abnormal if >1 were hyaline, granular, hyaline granular, or otherwise pathological. The absence of urinary crystals was defined as normal, whereas the presence of any uric acid, amorphous urate, calcium oxalate, triple phosphate, or amorphous phosphate crystals was considered abnormal.

Serum hCG levels ≥5 IU/L indicated pregnancy. BMI was calculated using the patient's weight in kilograms divided by the height in meters squared and was classified as underweight (<18.5), normal (18.5–), overweight (25–), and obese (30+). High blood pressure was defined as >140/90 mmHg in adults <60-year-old

and >150/90 mmHg in older adults. Diabetes mellitus was defined as fasting blood sugar ≥126 mg/dl or HbA1c ≥6.5%. The threshold values were 1.3 mg/dL for serum creatinine, 20 mg/dL for BUN, and 7 mg/dL for uric acid. A 25-hydroxy Vitamin D level between 20 and 50 ng/mL was considered normal, while a level <20 ng/mL was considered low. Regarding lipid profile, triglyceride levels ≥150 mg/dl were defined as abnormal, while HDL cholesterol concentrations <40 mg/dl and <50 mg/dl were considered abnormal in males and females, respectively. Total cholesterol ≥200 mg/dL was considered abnormal. LDL cholesterol was classified as optimal (<100 mg/dL), borderline (130–159 mg/dL), or high (>160 mg/dL). eGFR was calculated using the Modification of Diet in Renal Disease Study equation: EGFR = 175 × (SCr) - 1.154 × (age) - 0.203 × 0.742 (if female) × 1.212 (if Black). The results were classified as normal if the level was ≥60 mL/min/1.73 m^2 and abnormal if it was <60 mL/min/1.73 m^2, in which case it was defined as CKD. Statistical Package for Social Sciences (SPSS V. 26) (IBM Corp, Armonk, NY) software was used for the analysis. A Chi-square test was used to determine the association between proteinuria and other potential associated factors. A logistic regression model was performed to determine the independent factors associated with proteinuria (yes, no). The significant factors resulting from the bivariate analysis only were entered into the model as independent factors, and the results were considered statistically significant at $P < 0.05$.

Results

A total of 2942 urinalysis tests were examined, corresponding to patients/subjects who came to the clinics. The baseline demographic and laboratory characteristics are shown in Table 1. Of the sample, 68.8% were Saudi nationals, 62.3% were female (1832), and 152 were pregnant. The mean age of the subjects was 42.4 ± 14.5 years. Almost half (52.2%) were 40-year-old and above. The highest proportion of the subjects was obese (47.0%) and overweight (31.8%), while only 20% were normal weight; 1.3% were underweight. Of the subjects, 7.7% had high blood pressure, 21.2% had diabetes mellitus based on fasting glucose, and 47.8% based on HbA1c. Hyperuricemia was found in 9.5% and CKD (eGFR < 60) in 3.6% of the subjects. Abnormalities in total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were found in 39.7%, 11.1%, 8.2%, and 22.4% of the subjects, respectively. In addition, in 70.5% of subjects, 25-hydroxyvitamin D levels were deficient [Table 1].

Of the 2942 subjects, 7.1% had trace proteinuria (±), while 4.2% had overt proteinuria (≥1+). There was no statistically significant association between proteinuria and specific urinalysis abnormalities, including urinary specific gravity, pH, and the presence of bilirubin, ketones, ascorbic acid, leukocytes, WBCs, epithelial cells, yeast cells, crystals, trichomonas, and bacteria (not shown). There was a statistically significant association between proteinuria and some abnormal urinalysis components, including color, clarity, the presence of urobilinogen, glucose, blood, nitrite, RBCs, casts, and mucous threads ($P < 0.05$) [Table 2].

Proteinuria was significantly more prevalent in males (5.4%) than in females (3.5%) ($P < 0.015$). Only one of the 152 pregnant women had proteinuria. In subjects aged ≥ 40 years, proteinuria was more common (5.2% vs. 3.2%) ($P = 0.007$). For those with high systolic and diastolic blood pressure (DBP), the prevalence of proteinuria was 9.7% and 8.8%, respectively, compared to 4.4% and 4.5% in normotensives, indicating a significant association between proteinuria and high blood pressure. According to fasting glucose and HbA1c levels, the prevalence of proteinuria in diabetic patients was 8.7% and 8.0%, compared to 2.0% and 2.6% in normoglycemic subjects; both were significantly associated with proteinuria ($P < 0.0001$). Hyperuricemia was in 11.4% of subjects with overt proteinuria (≥1+). No significant association was found between uric acid and proteinuria. Creatinine was high in 32.2% of subjects with overt proteinuria. In CKD patients (eGFR <60), 29.3% had proteinuria compared to 3.9% of those with normal eGFR, with a significant association according to the bivariate analysis. Regarding lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), only LDL cholesterol was significantly associated with proteinuria, with a prevalence of 5.8%. The prevalence of proteinuria in subjects with deficient 25-hydroxyvitamin D levels was 5.3% ($P < 0.120$). The bivariate analysis showed a significant association between proteinuria and Saudi nationality, female gender, age ≥40 years, high systolic blood pressure, DBP, fasting glucose, HbA1c, BUN, and creatinine, low eGFR, and high LDL cholesterol. No significant association was found between proteinuria and BMI, uric acid, total cholesterol, HDL cholesterol, and triglycerides [Table 3].

Using the logistic regression model, the only variables that were independently associated with proteinuria were the presence of casts in the urine, Saudi nationality, high creatinine, and older age. About 28% of the variations in proteinuria can be explained by the variations in these variables. Adjusted odds ratios (OR) are shown in Table 4.

Discussion

This study revealed a proteinuria rate of 4.2% in Dammam, which is consistent with other reports in the literature, specifically in Malaysia, India, Nigeria,

Table 1: Baseline demographic and laboratory characteristics of patients attending the family medicine clinic in Dammam between January 2018 and January 2020

Characteristics	*N* (%)
Nationality (*n*=2942)	
Saudi	2023 (68.8)
Non-Saudi	919 (31.2)
Gender (*n*=2942)	
Male	1110 (37.7)
Female	1832 (62.3)
Pregnant (serum hCG ≥5 IU/L)	152 (8.3)
Age (*n*=2942)	
<40	1406 (47.8)
≥40	1536 (52.2)
BMI (*n*=2837)	
Underweight (<18.5 kg/m^2)	36 (1.3)
Normal (18.5–22.9 kg/m^2)	567 (20.0)
Overweight (25–29.9 kg/m^2)	902 (31.8)
Obese (≥30 kg/m^2)	1332 (47.0)
Blood pressure (*n*=1337)	
High SBP age <60 (>140 mmHg) - Age ≥60 (>150 mmHg)	103 (7.7)
High DBP age <60 (>90 mmHg) - Age ≥60 (>90 mmHg)	103 (7.7)
Fasting glucose (*n*=1683)	
Prediabetes (100–125 mg/dl)	514 (30.5)
DM (≥126 mg/dl)	356 (21.2)
HbA1c (*n*=1522)	
DM (≥6.5%)	728 (47.8)
Uric acid (*n*=463)	
Abnormal ≥7 mg/dl	44 (9.5)
Renal function test (*n*=2286)	
Abnormal BUN >20 mg/dl	31 (4.1)
Abnormal creatinine >1.3 mg/dl	62 (2.7)
Abnormal eGFR <60	82 (3.6)
25-hydroxy Vitamin D (*n*=755)	
Deficiency (<20 ng/mL)	532 (70.5)
Lipid profile (*n*=1540)	
Abnormal LDL cholesterol	
Near-optimal (100–129 mg/dl)	499 (32.4)
Borderline (130–159 mg/dl)	409 (26.6)
High (>160 mg/dl)	171 (11.1)
Abnormal HDL cholesterol males (<40) and females (<50 mg/dl)	126 (8.2)
Abnormal total cholesterol ≥200 mg/dl	611 (39.7)
Abnormal triglyceride ≥150 mg/dl	345 (22.4)

hCG=Human chorionic gonadotropin, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, BUN=Blood urea nitrogen, eGFR=estimated glomerular filtration rate, HDL=High-density lipoprotein, LDL=Low-density lipoproteins, DM=Diabetes mellitus, HbA1c=Glycated hemoglobin

Table 2: Association between proteinuria and other urinalysis components among patients attending family medicine clinic in Dammam between January 2018 and January 2020 (*n*=2942)

Urinalysis components	Negative *N* (%)	Overt proteinuria *N* (%)	*P-value*
Color			
Normal	2458 (96.2)	97 (3.8)	<0.0001
Dark yellow	295 (93.4)	21 (6.6)	
Amber	56 (91.8)	5 (8.2)	
Orange	1 (100.0)	0	
Red	0	1 (100.0)	
Brown	7 (87.5)	1 (12.5)	
Clarity			
Normal	2428 (96.2)	97 (3.8)	0.002
Cloudy	247 (95.0)	13 (5.0)	
Turbid	142 (90.4)	15 (9.6)	
Urobilinogen			
Negative	2700 (95.9)	115 (4.1)	0.038
Positive	117 (92.1)	10 (7.9)	
Glucose			
Negative	2659 (96.3)	103 (3.7)	<0.0001
Positive	158 (87.8)	22 (12.2)	
Blood			
Negative	1829 (97.5)	47 (2.5)	<0.0001
Positive	988 (92.7)	78 (7.3)	
Nitrite			
Negative	2761 (95.9)	118 (4.1)	0.006
Positive	56 (88.9)	7 (11.1)	
RBC			
Normal	1862 (97.2)	53 (2.8)	<0.0001
≥3 RBC/HPF	955 (93.0)	72 (7.0)	
Casts			
0–1	2736 (96.5)	99 (3.5)	<0.0001
>1	81 (75.7)	26 (24.3)	
Mucus threads			
Not seen or rare	1129 (94.9)	61 (5.1)	0.052
Positive	1688 (96.3)	64 (3.7)	

RBC=Red blood cell, HPF=High-power field

and Japan, with rates ranging from 1.2% to 18.9%.[14-18] However, the rate in the current study is lower than what has been reported in many other populations (8%–33%).[2] The variation in percentages could be due to the false-positive and false-negative results of dipstick urinalysis.[17] Moreover, proteinuria should be verified in cases with transient causes.[18]

In Saudi Arabia, the prevalence of hypertension and diabetes mellitus is 25.5%[19] and 23.9%,[20] respectively. Although many previous studies have demonstrated a significant association between proteinuria and high blood pressure and high blood glucose,[4,17,18,21] they were considered confounding factors in this study after applying the logistic regression model. Moreover, in a study involving subjects between 20 and 39 years of age, high blood glucose had the highest OR for proteinuria (adjusted OR: 13.591, 95% CI: 5.897–31.327).[12] The combination of high blood sugar and high blood pressure significantly increases the risk of proteinuria.[18] Most primary and secondary kidney diseases are more common in men than women, and persistent proteinuria is twice as common in men as in women.[2] In the current study, the prevalence of proteinuria was higher in men (5.4%) than in women (3.5%). Unexpectedly, no

Table 3: Association between proteinuria and demographic and laboratory variables among patients attending family medicine clinic in Dammam between January 2018 and January 2020

Variable	Negative *N* (%)	Overt proteinuria *N* (%)	*P-value*
Nationality			
Saudi	1927 (95.3)	96 (4.7)	0.048
Non-Saudi	890 (96.8)	29 (3.2)	
Gender			
Male	1050 (94.6)	60 (5.4)	0.015
Female	1767 (96.5)	65 (3.5)	
Age			
<40	1361 (96.8)	45 (3.2)	0.007
≥40	1456 (94.8)	80 (5.2)	
SBP			
Normal	1180 (95.6)	54 (4.4)	0.015
High SBP	93 (90.3)	10 (9.7)	
DBP			
Normal	1179 (95.5)	55 (4.5)	0.047
High DBP	93 (91.2)	9 (8.8)	
Fasting glucose			
Normal	792 (97.4)	21 (2.6)	<0.0001
Prediabetes (100–125 mg/dl)	497 (96.7)	17 (3.3)	
DM (≥126)	325 (91.3)	31 (8.7)	
HbA1c			
Normal	778 (98.0)	16 (2.0)	<0.0001
DM (≥6.5%)	670 (92.0)	58 (8.0)	
BUN			
Normal	2162 (95.9)	92 (4.1)	<0.0001
>20 mg/dl	14 (45.2)	17 (54.8)	
Creatinine			
Normal	2135 (96.0)	89 (4.0)	<0.0001
>1.3 mg/dl	42 (67.7)	20 (32.3)	
eGFR			
≥60 normal	2119 (96.1)	85 (3.9)	<0.0001
<60 CKD	58 (70.7)	24 (29.3)	
LDL-cholesterol			
Optimal<100 mg/dl	425 (92.2)	36 (7.8)	0.001
Near-optimal (100–129 mg/dl)	479 (96.0)	20 (4.0)	
Borderline (130–159 mg/dl)	400 (97.8)	9 (2.2)	
High (>160 mg/dl)	161 (94.2)	10 (5.8)	

SBP=Systolic blood pressure, DBP=Diastolic blood pressure, BUN=Blood urea nitrogen, eGFR=estimated glomerular filtration rate, LDL=Low-density lipoproteins, DM=Diabetes mellitus, HbA1c=Glycated hemoglobin, CKD=Chronic kidney disease

Table 4: Logistic regression analysis: Factors associated with the presence of proteinuria

	β	SE	Wald	df	Significance	Odds Ratio (OR)	95% CI for OR	
							Lower	Upper
Casts	2.667	0.798	11.160	1	0.001	14.393	3.011	68.808
Saudi nationality	2.042	0.949	4.627	1	0.031	7.709	1.199	49.565
Age	0.066	0.023	8.242	1	0.004	1.068	1.021	1.117
Creatinine	1.656	0.807	4.209	1	0.040	5.241	1.077	25.507

Hosmer and Lemeshow χ^2=7.6, P=0.47, Cox and Snell R^2=0.103, Nagelkerke R^2=0.289. SE=Standard error, CI=Confidence interval

significant association between gender and proteinuria was indicated by the logistic regression model. However, a similar result has been reported in other studies.[12,15,17,21]

High triglyceride and low HDL cholesterol levels were not significantly associated with proteinuria ($P < 0.366$ and $P < 0.421$, respectively) although both are reported to be linked to the risk of greater proteinuria.[11] Based on the bivariate analysis, LDL cholesterol was significantly associated with proteinuria ($P < 0.001$), but not after the logistic regression model. No link between LDL cholesterol and proteinuria has been reported in other studies.

Proteinuria is a common and essential predictor of CKD, and it is associated with end-stage renal disease and increased mortality.[22] Estimated GFR levels below 60 mL/min/1.73 m indicate CKD.[23] Moreover, previous studies have reported an association between increased prevalence of proteinuria with lower eGFR levels.[16,24] Although this study revealed no significant association between proteinuria and eGFR using the logistic regression model, the significant association between proteinuria rates and high creatinine levels is worth noting. Measuring serum creatinine is a first step in the assessment of eGFR using the creatinine-based equation.[23] It has been reported that CKD might be missed if only dipstick proteinuria is used for screening. Thus, it is advisable to use both proteinuria and serum creatinine in screening for CKD.[25]

A commonly found and nonspecific cast named hyaline can be seen in small volumes in concentrated urine or with the use of diuretic medications.[9,26] RBCs, WBCs, epithelial, granular, waxy, fatty, or broadcasts are pathological and indicate renal and glomerular diseases.[9,26] In the present study, among other risk factors, the presence of casts in urine was the factor most strongly associated with proteinuria (OR: 14.393, 95% CI: 3.011–68.808). A previous study reported a significant increase in casts with increasing severity of proteinuria.[27]

Proteinuria is not a normal aging process, although a creatinine clearance of about 0.75 ml/min/year is a normal physiological reduction of creatinine clearance.[28] The current study showed an association between proteinuria and advancing age. Several studies have demonstrated similar findings.[15,17,21] For example, an increase of 3% in the odds of proteinuria was found with each year of increasing age.[15] These findings are in contrast with those of a study that showed an independent correlation between a lower risk of proteinuria and increasing age.[12,29]

The regression model was only able to explain 10% of the variations in proteinuria in this study. The model showed that Saudi nationality, advancing age, elevated serum creatinine levels, and casts in the urine were associated with proteinuria. Being a Saudi was the strongest predictor after urinary casts, increasing the risk of proteinuria sevenfold compared to the other studied factors. However, no association was revealed between proteinuria and the Saudi adult population in previous literature. Future studies should thus consider this finding. In addition, more variables that may be associated with proteinuria should be explored.

There were some limitations in this study. First, it was not possible to rule out false-positive proteinuria or consider transient proteinuria, since urinalysis should be done 24 h after vigorous exercise or acute illness.[30] Second, it was not possible to confirm the presence of chronic diseases such as diabetes mellitus, hypertension, and CKD from the data (i.e., medication and file documentation). Third, we did not know whether the study subjects with proteinuria were symptomatic. This would provide valuable information in the consideration of the use of urine dipsticks as a screening tool for proteinuria.

Conclusion

This study found that proteinuria was significantly associated with Saudi nationality, age 40 years and above, elevated serum creatinine levels, and the presence of casts in urine. These findings should be borne in mind by primary healthcare practitioners to expedite the prompt detection of proteinuria in urinalysis. Practitioners should also look for proteinuria in female, diabetic, hypertensive, CKD, and high LDL cholesterol patients.

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Conflicts of interest

There are no conflicts of interest.

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