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Proteinuria and Reduced Estimated Glomerular Filtration Rate Independently Predict Risk for Acute Myocardial Infarction: Findings from a Population-Based Study in Keelung, Taiwan

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Background: The aim of this study was to evaluate the independent roles of proteinuria and reduced estimated glomerular filtration rate (GFR) in the development of acute myocardial infarction in a northern Taiwanese population.
Methods: We conducted a community-based prospective cohort study in Keelung, the northernmost county of Taiwan. A total of 63,129 subjects (63% women) ≧ 20 years of age who had no history of coronary heart disease were recruited and followed-up. Univariate and multivariate proportional hazards regression analysis was performed to assess the association between proteinuria and estimated GFR and the risk of acute myocardial infarction.
Results: There were 305 new cases of acute myocardial infarction (114 women and 191 men) documented during a four-year follow-up period. After adjustment of potential confounding covariates, heavier proteinuria (dipstick urinalysis reading 3+) and estimated GFR of less than 60 ml/min/1.73 m^2 independently predicted increased risk of developing acute myocardial infarction. The adjusted hazard ratio (aHR) of heavier proteinuria for occurrence of acute myocardial infarction was 1.85 [95% confidence intervals (CI), 1.17-2.91, $p < 0.01$] (vs. the reference group: negative dipstick proteinuria). The aHR of estimated GFR of 30-59 ml/min/1.73 m^2 for occurrence of acute myocardial infarction was 2.4 (95% CI, 1.31-4.38, $p < 0.01$) (vs. the reference group: estimated GFR ≧ 90 ml/min/1.73 m^2), and that of estimated GFR of 15-29 ml/min/1.73 m^2 was 5.26 (95% CI, 2.26-12.26, $p < 0.01$).
Conclusions: We demonstrated that both heavier proteinuria and lower estimated GFR are significant independent predictors of developing future acute myocardial infarction in a northern Taiwanese population.

Key Words: Acute myocardial infarction • Estimated glomerular filtration rate • Proteinuria

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INTRODUCTION

The traditional major risk factors for coronary heart disease (CHD) such as elevated blood pressure, cholesterol, diabetes mellitus, tobacco smoking and obesity have been well-studied and established.[1,2] However, treatment of these risk factors with medication and lifestyle modification has led to a substantial decrease in the risk of CHD.[1,2]

Meanwhile, in the past years a substantial number of studies have examined several additional important risk factors for CHD, including level of kidney dysfunction. Estimated glomerular filtration rate (GFR), a com-

monly used marker of kidney function, is able to predict cardiovascular events and mortality not only in patients with high risk for cardiovascular disease but also in the general population.[3,4] Proteinuria is a powerful factor for predicting kidney dysfunction, and has also been proven to be associated with an increased risk for adverse cardiovascular outcomes.[5] However, scant few reports have evaluated the predictive value and independent role of proteinuria and reduced estimated GFR simultaneously in the development of the major cardiovascular event – acute myocardial infarction (AMI) in the general population.[6] Furthermore, our understanding of the relative significance of these two risk factors and the impact of them on CHD risk comes primarily from studies that examined Caucasian populations.[3-6]

CHD incidence and prevalence in Taiwan, a newly developed region of rapidily changing lifestyles accompanied by modernization and westernization, continues to rise.[7] One of the main causes of death in Taiwan now is CHD or AMI, although CHD mortality rate is still lower than that in Western countries. The aim of the present study was to assess whether both proteinuria and reduced estimated GFR independently predicted future AMI in a community-based cohort in a northern Taiwan population. The results of the present large prospective cohort may provide the necessary evidence associated with just how important renal factors can be to predicting major cardiovascular outcomes in Asian populations.

MATERIALS AND METHODS

Study population and design

All study participants were enrolled in the Keelung community-based integrated screening (KCIS) program, which was carried out in Keelung, the northernmost county of Taiwan. The details of the original design of the study, implementation, and some early results from the KCIS program have been published previously.[8] Briefly, the KCIS program was initially conducted to invite women who had not undergone a Pap smear within 3 years prior to the beginning of the program for screening for 5 types of neoplastic diseases and 3 types of chronic diseases; their relatives aged 20 years or above were then welcomed to take part in the study. In the KCIS program, information on multiple factors generally considered to be associated with increased risk of CHD were gathered, so these data enabled us to examine the independent effect of proteinuria and decreased estimated GFR on the occurrence of AMI. In the present prospective study, subjects with previously diagnosed CHD upon recruitment were excluded. During the period of annual recruitment screening between 2001 and 2004, a total of 63,129 participants who gave written informed consent were eligible for inclusion in the current cohort study.

Data collection

The baseline data collected at each recruitment screening by trained personnel included the following. Information about smoking status and personal medical history was collected from a structured questionnaire. Biochemical variables, such as fasting plasma glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen, creatinine, and uric acid, and anthropometric measures, such as waist circumference, body mass index and blood pressure were obtained. Systolic and diastolic blood pressure were recorded by which the individual hypertensive status was determined according to the JNC 7 classification. A random spot urine specimen was used to assess proteinuria by urinary dipstick tests. Proteinuria was divided into five groups (-, +/-, 1+, 2+, 3+). The estimated GFR was calculated by the Modification of Diet in Renal Disease Study equation.[9] Subjects were stratified into five categories of estimated GFR levels (≥ 90, 89-60, 59-30, 29-15, < 15 ml/min/1.73 m^2). We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to define AMI (ICD-9-CM 410).

Statistical analysis

The main outcome of notable interest in the present investigation was the occurrence of newly developed AMI during the study's four-year follow-up. We used univariate analysis first with the proportional hazards regression model to estimate the strength of the association between various possible risk factors and events of AMI. Additionally, hazard ratios (HRs) and their 95% confidence intervals (CI) were calculated. The multivariate proportional hazards regression analysis was then performed to estimate the adjusted HRs for pro-

teinuria and decreased estimated GFR after adjustment for other available confounding factors recognized in the univariate analyses, which included gender, age, hypertension, fasting glucose, body mass index, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, uric acid, waist, and smoking.

RESULTS

A total of 39,486 women and 23,643 men were included in the analysis. During a four-year follow-up period, we documented 305 cases of first AMI, consisting of 114 women and 191 men. The baseline characteristics of the participants are shown in Table 1. The pa-

Table 1. Demographic features for subjects attending Keelung community-based integrated screening program, 2001-2004

Variable			Case of AMI	
	N (n = 63129)	%	N (n= 305)	‰
Gender				
male	23643	37.45	191	8.08
female	39486	62.55	114	2.89
Age group				
20-29	5057	8.01	0	0
30-39	12610	19.97	6	0.48
40-49	15733	24.92	21	1.33
50-59	11955	18.94	41	3.43
60-69	10458	16.57	107	10.23
70-79	7316	11.59	130	17.77
Hypertension				
Normal	25853	41.6	66	2.55
Prehypertension	23495	37.8	118	5.02
Stage 1	9281	14.93	82	8.84
Stage 2	3520	5.66	36	10.23
Missing	980		3	
DM				
No	52939	86.41	204	3.85
Yes	3724	6.08	61	16.38
Not aware	4605	7.52	24	5.21
Missing	1861		16	
Proteinuria				
(-)	42342	83.93	159	3.76
(+/-)	3424	6.79	29	8.47
(+)	2284	4.53	27	11.82
(++)	1521	3.02	22	14.46
(+++)	876	1.74	23	26.26
Missing	12682		45	

Table 1. Continued

Variable			Case of AMI	
	N (n = 63129)	%	N (n= 305)	‰
AC sugar				
< 110	54700	88.38	192	3.51
110-125	2922	4.72	29	9.92
≧ 126	4293	6.93	73	17
Missing	1214		11	
BMI				
< 25	37579	60.28	132	3.51
25-29	20036	32.14	135	6.74
≧ 30	4723	7.58	35	7.41
Missing	791		3	
Cholesterol				
< 200	36035	58.19	145	4.02
200-239	18192	29.38	89	4.89
≧ 240	7698	12.43	60	7.79
Missing	1204		11	
TG				
< 150	45903	74.13	164	3.57
150-199	7204	11.63	55	7.63
≧ 200	8818	14.24	75	8.51
Missing	1204		11	
LDL-C				
< 100	21424	34.79	83	3.87
100-159	34470	54.6	167	4.84
≧ 160	5690	9.01	39	6.85
Missing	1545		16	
HDL-C				
< 40	7290	11.77	67	9.19
40-59	32146	51.91	150	4.67
≧ 60	22489	36.32	77	3.42
Missing	1204		11	
CCr				
≧ 90	22205	36.18	24	1.08
89-60	29848	48.63	96	3.22
59-30	8950	14.58	161	17.99
29-15	289	0.47	12	41.81
< 15	86	0.14	0	0
Missing	1751		12	
Waist				
Normal	42870	69.13	152	3.55
Abnormal	19148	30.87	150	7.83
Missing	1111		3	
Uric acid				
Normal	41387	66.83	117	2.86
Abnormal	20538	33.17	177	8.62
Missing	1204		11	
Smoking				
Never	443745	73.08	177	4.05
Ever use	16110	26.92	86	6.23
Missing	3632		16	

AMI, acute myocardial infarction; BMI, body mass index; CCr, creatinine clearance rate; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol, LDL-C, low-density lipoprotein-cholesterol, TG, triglyceride.

tients with MI were generally older, more male gender and a higher percentage of them had conventional risk factors for CHD such as hypertension, diabetes and hypercholesterolemia.

Table 2 displays the result of univariate analysis evaluating the independent role of various factors. In addition to other well-known risk factors of AMI as shown in Table 2, subjects with proteinuria and estimated GFR of less than 90 ml/min/1.73 m^2 also had a higher risk for developing AMI. The impact of proteinuria could be found even in those patients with minimal proteinuria (dipstick urinalysis reading 1+) [HR = 1.85 (1.23-2.79)], but the effect was substantially increased in those with heavier proteinuria (dipstick urinalysis reading 3+) [HR = 3.82 (2.47-5.90)]. A dose-effect phenomenon was also found in estimated GFR. The HRs for developing AMI exponentially increased as estimated GFR decreased (HRs from 2.72 to 15.56 and to 50.88 with decreasing GFR).

In the multivariable analysis after adjusting for other available confounding variables, the effect of proteinuria and reduced estimated GFR were still present, but the HRs decreased compared to those in univariate analysis. Furthermore, only heavier proteinuria (dipstick urinalysis reading 3+) and estimated GFR of less than 60 ml/min/1.73 m^2 independently predicted increased risk of developing AMI. The adjusted HR of heavier proteinuria for occurrence of AMI was 1.85 (95% CI, 1.17-2.91, $p < 0.01$) (vs. the reference group: negative dipstick proteinuria). Dose-effect phenomenon was still found after multivariable adjustment for estimated GFR. The adjusted HR of estimated GFR of 30-59 ml/min/1.73 m^2 for occurrence of AMI was 2.4 (95% CI, 1.31-4.38, $p < 0.01$) (vs. the reference group: estimated GFR $\geqq$ 90 ml/min/1.73 m^2), and that of estimated GFR of 15-29 ml/min/1.73 m^2 was 5.26 (95% CI, 2.26-12.26, $p < 0.01$).

DISCUSSION

In this community-based cohort study of 63,129 participants aged 20-79 years, we demonstrated that both heavier proteinuria (dipstick urinalysis reading 3+) and lower estimated GFR (less than 60 ml/min/1.73 m^2) contributed independently to the risk of developing AMI after adjustment for confounding variables in a northern Taiwanese population. To the best of our knowledge, this present report is the first large-scale population-based prospective study elucidating directly the significant role of both proteinuria and reduced estimated GFR in the increased risk for subsequent AMI in an Asian population.

Recently, proteinuria/albuminuria is known not only as a sensitive risk factor for the progression of kidney disease but also as a strong predictor of cardiovascular risk in patients with diabetes mellitus or hypertension and even in the general populations.[5,10] With regard to CHD, a recent meta-analysis indicated that proteinuria/albuminuria was associated with an increased risk independently of other conventional risk factors for CHD.[11] However, among these included reports only two studies were both designed with controlling the confounder of kidney dysfunction (reduced GFR) and carried out in the general population.[12,13] In one study in a Western population, an increased risk for CHD was discovered in patients with minimally elevated albuminuria below the currently accepted level of microalbuminuria.[13] A dose-response correlation between levels of excretion of urinary albumin and the risk of future CHD events was observed in the meta-analysis.[11] However, some studies did not show such a linear relationship between levels of albuminuria and cardiovascular risk.[14,15] Instead, there seems to be a given level of proteinuria/albuminuria as a threshold beyond which the relationship becomes significant, as shown in the present study.

In contrast to previous reports, the unique feature in this present study was that we found only heavier proteinuria (dipstick urinalysis reading 3+) was an independent indicator of development of AMI. In our report, heavier proteinuria was associated with a 1.85-fold higher risk after adjusting for other CHD risk factors, including impairment of kidney function. The magnitude of this association is close to that in the case of macroalbuminuria reported in the meta-analysis.[11] Although the heavier proteinuria and macroalbuminuria have different units and meanings, they are both important markers to indicate renal impairment. We measured proteinuria using a urine dipstick test, which was considered a less favorable modality than urine albumin-creatinine ratio or urine albumin excretion. But previous studies have shown compatible abilities in evaluating

Table 2. Result of proportional hazards regression model for developing AMI of subjects attending Keelung Community-based Integrated Screening program, 2001-2004

Variable	Univariate model			Multivariate model		
	HR	95% CI	p	aHR	95% CI	p
Gender						
Male	2.89	2.27-3.68	< 0.001	1.49	1.07-2.08	0.001
Female	1			1		
Age group						
20-49	1			1		
50-59	4.35	2.67-7.09	< 0.001	3.51	2.00-6.15	0.002
60-69	11.43	7.49-17.46	< 0.001	5.78	3.26-10.23	0.001
70-79	16.71	10.96-25.46	< 0.001	7.89	4.30-14.50	< 0.001
Hypertension						
Normal	1			1		
Prehypertension	2.26	1.66-3.09	0.003	1.02	0.74-1.41	0.10
Stage 1	3.35	2.26-5.96	< 0.001	0.98	0.68-1.40	0.08
Stage 2	3.55	2.86-8.88	< 0.001	0.94	0.60-1.48	0.08
Proteinuria						
(-)	1			1		
(+/-)	1.85	1.23-2.79	0.009	1.42	0.95-2.14	0.09
(+)	1.97	1.30-3.00	0.007	1.29	0.84-1.98	0.08
(++)	1.97	1.21-3.20	0.007	1.18	0.73-1.91	0.08
(+++)	3.82	2.47-5.90	< 0.001	1.85	1.17-3.86	0.002
AC sugar						
<110	1			1		
110-125	2.03	1.36-3.03	0.005	1.27	0.85-1.90	0.08
≧ 126	4.26	3.29-5.52	< 0.001	2.17	1.64-2.86	0.001
BMI						
<25	1			1		
25-29	1.84	1.43-2.36	0.008	1.19	0.88-1.61	0.10
≧ 30	2.18	1.49-3.19	0.002	1.11	0.68-1.82	0.09
Cholesterol						
<200	1			1		
200-239	1.33	1.01-1.75	0.009	1.03	0.73-1.44	0.07
≧ 240	2.08	1.53-2.84	0.004	1.42	0.85-2.39	0.06
TG						
<150	1			1		
150-199	2.38	1.74-3.26	0.009	0.93	0.66-1.3	0.10
≧ 200	2.71	2.04-3.61	0.005	0.94	0.66-1.33	0.09
LDL-C						
<100	1			1		
100-159	1.7	1.29-2.25	0.008	1.18	0.84-1.64	0.08
≧ 160	2.83	1.90-4.21	0.003	1.45	0.79-2.65	0.07
HDL-C						
<40	1			1		
40-59	0.23	0.17-0.31	0.002	0.34	0.24-0.48	0.001
≧ 60	0.11	0.07-0.15	0.001	0.23	0.15-0.35	< 0.001
CCr						
≧ 90	1			1		
89-60	2.72	0.74-4.25	0.07	1.14	0.67-1.94	0.05
59-30	15.56	10.13-23.92	< 0.001	2.4	1.31-4.38	0.008
29-15	50.88	25.44-101.78	< 0.001	5.26	2.26-12.26	< 0.001
<15	0			0		
Waist						
Normal	1			1		
Abnormal	2.07	1.64-2.62	0.008	1.05	0.77-1.43	0.09
Uric acid						
Normal	1			1		
Abnormal	3.27	2.56-4.16	0.002	1.52	1.15-2.01	0.003
Smoking						
Never	1			1		
Ever use	1.88	1.48-2.37	0.006	1.1	0.81-1.48	0.07

AMI, acute myocardial infarction; BMI, body mass index; CI, confidence interval; CCr, creatinine clearance rate; HDL-C, high-density lipoprotein-cholesterol, HR, hazard ratio; LDL-C, low-density lipoprotein-cholesterol, TG, triglyceride.

cardiovascular risk and providing prognostic information.[6,11] In addition, the strength of such relationship between proteinuria/albuminuria and CHD risk appears to be affected by varied racial groups and populations with different levels of risk for CHD. One prospective cohort study in an ethnically diverse United Kingdom population and another in a population in Mexico had shown that the predictive power of albuminuria for adverse CHD outcomes differed by ethnicity.[16,17]

Although proteinuria/albuminuria is considered a surrogate marker of inflammatory process and abnormal endothelial function, the mechanisms underlying proteinuria/albuminuria as an independent risk factor of CHD or cardiovascular events remain unclear.[5] The possible explanations involve the question of whether proteinuria/albuminuria is the cause or consequence of generalized endothelial damage. Among apparently healthy individuals a different amount of albuminuria is found, reflecting interindividual variations in renal and systemic microvascular endothelial regulation. Such inherited distinction would result in varying degrees of individual vulnerability to develop future renal and cardiovascular damage. On the other hand, proteinuria/albuminuria often clusters other cardiovascular risk factors and thus as an early sign of endothelial dysfunction and the presence of proteinuria/albuminuria may just reflect the clinical settings of uncontrolled, unrevealed these risk factors.

Reduced GFR and proteinuria are viewed as two main manifestations of chronic kidney disease. Over the past years, epidemiological evidence has indicated that reduced estimated GFR is associated with an increased risk for CHD events and associated mortality in high-risk and even the general populations.[4,18] However, most of these studies did not take into account the potential confounding impact of proteinuria/albuminuria on CHD risk and that could lead to a misestimate of the true risk caused by reduced estimated GFR itself. In the present study in the Taiwanese general population, we demonstrated that for people with estimated GFR of 30-59 ml/min/1.73 m^2 and 15-29 ml/min/1.73 m^2 the risk of developing AMI was 2.4-fold and 5.3-fold higher, respectively, in comparison with those with estimated GFR of 90 ml/min/1.73 m^2 or greater after adjusting for other CHD risk factors, including proteinuria. The strength of the relationship is stronger than that reported in most other previous studies, especially in the group of people with an estimated GFR of 15-29 ml/min/1.73 m^2.

Similar to proteinuria/albuminuria, it is interesting that reduced estimated GFR may have a distinct predictive effect on CHD outcomes in varied racial groups and populations with different degrees of risk for CHD. In low-risk general populations, results from published studies had revealed some conflicts about the relationship between kidney dysfunction and CHD risk.[19,20] The causes of why patients with reduced estimated GFR have a raised risk of CHD are also not completely clarified. Chronic kidney disease is related to a status of elevated inflammatory responses, oxidative stress and raised levels of thrombogenic factors, which participate in and accelerate the process of systemic atherosclerosis resulting in various cardiovascular diseases.[4]

On the basis of a growing amount of evidence from previous investigations, our data reinforced the recognition of both proteinuria and reduced estimated GFR as potential major predictors of CHD events. Therefore, incorporation of information about the occurrence and severity of proteinuria/albuminuria and reduced estimated GFR into the risk stratification for CHD in the general Taiwanese or other populations would improve the accuracy of predictive power. The guideline had certainly addressed the importance of the level of estimated GFR and the magnitude of proteinuria/albuminuria to overall and cardiovascular mortality.[21] However, among diverse ethnic groups, further research to better clarify the discrepancies in the ability of proteinuria/albuminuria and reduced estimated GFR to predict CHD risk may be needed.

Limitations

Our study also had certain limitations. First of all, in the models we used, we did not adjust for other important confounding factors such as socioeconomic status, physical activity, dietary behavior and inflammatory markers. Second, owing to the nature of study design, the final results would be confounded with the treatment effect. Particularly, the antihypertensive agents have effects on the level of proteinuria and estimated GFR. Third, some of proteinuria and estimated GFR values were missing. The present results assumed that the data missed was completely at random. Fourth, we used a single random urine specimen in evaluation

of proteinuria by urine dipstick test, which is a semi-quantitative and less precise measurement. Meanwhile, excretion of urinary protein may vary from day to day which could cause misclassification of proteinuria categories. These possible measurement inaccuracies could tend to underestimate the extent of the relationship between proteinuria and CHD risk.[22] Although the dipstick urinalysis is relatively insensitive, it is more feasible, effective and less expensive for large population-based screening.

CONCLUSIONS

In conclusion, we demonstrated that both heavier proteinuria and lower estimated GFR are significant independent predictors of developing AMI in a northern Taiwanese population. The results are basically in accordance with the findings in previous work and support the combined use of both proteinuria and estimated GFR in assessing an individual's risk for CHD and identifying patients at high risk who may benefit from early, aggressive interventions.

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