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【 ORIGINAL ARTICLE 】

Impact of Chronic Kidney Disease on Aortic Disease-related Mortality: A Four-year Community-Based Cohort Study

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Abstract:

Objective Despite advances in medicine, aortic diseases (ADs), such as aneurysm rupture and aortic dissection, remain fatal and carry extremely high mortality rates. Due to its low frequency, the risk of developing AD has not yet been fully elucidated. Chronic kidney disease (CKD) is an established risk factor for cardiovascular disease and mortality. The aim of the present study was to examine whether or not CKD is a risk for AD-related mortality in the general population.

Methods We used a nationwide database of 554,442 subjects (40-75 years old) who participated in the annual "Specific Health Check and Guidance in Japan" checkup between 2008 and 2013.

Results There were 131 aortic aneurysm and dissection deaths during the follow-up period of 2,123,512 person-years. A Kaplan-Meier analysis revealed that subjects with CKD had a higher rate of AD-related deaths than those without it. A multivariate Cox proportional hazard regression analysis demonstrated that CKD was an independent risk factor for AD-related death in the general population after adjusting for cardiovascular risk factors. The addition of CKD to cardiovascular risk factors significantly improved the C, net reclassification, and integrated discrimination indexes.

Conclusion CKD is an additional risk for AD-related death, suggesting that CKD may be a target for the prevention and early identification of subjects at high risk for AD-related death in the general population.

Key words: chronic kidney disease, aortic disease, general population

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Introduction

Aortic diseases (ADs), namely aortic aneurysm rupture and aortic artery dissection, are major causes of sudden death (1, 2). Notably, AD is the third-most common cause of sudden death according to autopsy data in Japan (3). Despite advances in medicine, it is still difficult to save a life after the onset of AD, since almost all people who suffer from AD die before hospital arrival (4). Furthermore, the mortality rate of AD at 1 month after symptom onset is approximately 50% despite treatment (5, 6). Therefore, it is critical to identify high-risk subjects and prevent the development of AD in the general population using health checkups.

Chronic kidney disease (CKD) is a well-known risk factor for cardiovascular disease and mortality, such as ischemic heart disease, heart failure, and stroke (7-9). Accumulating evidence indicates that CKD promotes atherosclerosis and cardiac dysfunction via endothelial dysfunction, volume expansion, cytokine secretion, sympathetic nervous activation, anemia, inflammation, and renin-angiotensin-aldosterone

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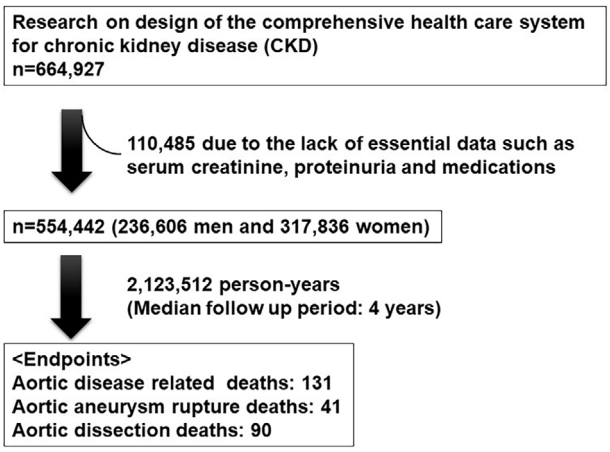

Figure 1. **The flow chart of the study selection process.**

system activation (10-14). Several cross-sectional studies have reported the relationship between abdominal aortic aneurysm and glomerular damage (15, 16). The Atherosclerosis Risk in Communities (ARIC) study prospectively indicated that CKD, defined as a reduced estimated glomerular filtration rate (eGFR) and microalbuminuria, is associated with incident abdominal aortic aneurysm in subjects who were mainly white or black (17). However, these studies started in the 1990s in the United States and Europe, and studies in Asian populations are lacking. Furthermore, there have been no reports examining the association of CKD with aortic dissection death in the general population. Therefore, the impact of CKD on the AD-related mortality in an Asian general population has not yet been fully elucidated.

The present study aimed to examine whether CKD is a novel risk factor for AD-related death in Japanese general population.

Materials and Methods

The manuscript was drafted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational study (18).

Study population

This study is a part of an ongoing "Research on design of the comprehensive health care system for CKD" based on individual risk assessments by the Specific Health Checkup for all inhabitants of Japan between 40 and 74 years old and is covered by the Japanese national health insurance system.

We utilized data obtained from the following seven prefectures (i.e., administrative regions): Fukushima, Niigata, Ibaraki, Osaka, Fukuoka, Miyazaki and Okinawa. We collected data from 284,321 men and 380,606 women (total, 664,927; age range, 40-74 years old) who participated in health checkups from 2008-2013. Among the 664,927 individuals, 110,485 were excluded from this study due to a lack of essential data, including serum creatinine, proteinuria, and medications. Therefore, 236,606 men and 317,836 women were included in our study. The flow chart of the study selection process is shown in Fig. 1.

Definition of cardiovascular risk

Hypertension (HT) was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or antihypertensive medication use. Diabetes mellitus (DM) was defined as a fasting blood glucose ≥126 mg/dL, glycosylated hemoglobin A1c (HbA1c) ≥6.5% (National Glycohemoglobin Standardization Program), or anti-diabetic medication use. Dyslipidemia (DL) was defined as high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, triglyceride ≥150 mg/dL, or lipid-lowering medication use.

Definition of CKD

Serum creatinine was measured using an enzymatic method, while the eGFR was calculated using the modification of diet in renal disease equation with the Japanese coefficient (19). A urinalysis was performed with the dipstick measurement of a single spot urine specimen collected at the health checkup. The results were recorded as negative, trace, 1+, 2+, or 3+. Proteinuria was defined as a value ≥1+. CKD was defined as a reduced eGFR (<60 mL/min/1.73 m^2) or the presence of proteinuria according to the previous report (20).

Measurements

Fasting blood sugar (FBS), HbA1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were measured. All blood and urine analyses were performed at the local laboratories. The methods for the analyses were not standardized between laboratories. However, the analyses were based on the Japan Society of Clinical Chemistry recommended methods for laboratory tests, which have been widely accepted by laboratories across Japan.

Endpoint and follow-up

After obtaining permission from the Ministry of Health, Labour and Welfare, we accessed the database containing death certificates for all deaths that occurred between 2008 and 2015 in Japan. All subjects were prospectively followed for a median of 1,456 days (interquartile range, 993-1,830 days). Subjects who survived were followed until they reached 75 years old. The endpoint was AD-related death, such as aortic aneurysm rupture and aortic dissection. The cause of death was determined by reviewing the death certificates and classified based on the death code (International Classification of Diseases, 10th Revision). Death from rupture of aortic aneurysm was defined as the death code [I71.1], [I71.3], and [I71.8]. Death from aortic dissection was defied as the death code [I71.0].

Statistical analyses

The normality of continuous variables was checked by the Kolmogorov-Smirnov-Lillefors test. Continuous and cate-

Table 1. Comparison of Clinical Characteristics between Subjects with and without CKD.

Variables	All subjects n=554,442	CKD (-) n=452,612	CKD (+) n=101,830	p value
Age	62.8±8.7	62.2±8.9	65.7±7.2	<0.0001
Male, n (%)	236,606 (43%)	182,006 (40%)	54,600 (54%)	<0.0001
BMI, kg/m^2	23.4±3.5	23.2±3.4	24.2±3.6	<0.0001
Hypertension, n (%)	327,379 (59%)	255,529 (56%)	71,850 (71%)	<0.0001
Diabetes mellitus, n (%)	51,793 (9.3%)	37,367 (8.3%)	14,426 (14.2%)	<0.0001
Dyslipidemia, n (%)	272,441 (49%)	215,052 (48%)	57,389 (56%)	<0.0001
Smoking, n (%)	84,227 (15%)	70,132 (16%)	14,095 (14%)	<0.0001
Biochemical data				
Creatinine (mg/dL)	0.72±0.39	0.67±0.13	0.96±0.87	<0.0001
eGFR (mL/min/1.73m^2)	75.6±15.4	79.5±15.4	58.3±15.3	<0.0001
HbA1c (%)	5.4±0.7	5.4±0.7	5.5±0.9	<0.0001
Fasting blood sugar (mg/dL)	98±21	97±20	102±26	<0.0001
Proteinuria, n (%)	32,452 (5.9%)	0 (0%)	32,452 (32%)	<0.0001
Reduced eGFR, n (%)	78,972 (14%)	0 (0%)	78,972 (78%)	<0.0001
CKD, n (%)	101,830 (18%)			
Medications				
Anti-hypertensive drug, n (%)	166,049 (30%)	121,903 (27%)	44,146 (43%)	<0.0001
Anti-diabetic drug, n (%)	30,585 (5.5%)	21,422 (4.7%)	9,163 (9.0%)	<0.0001
Anti-dyslipidemia drug, n (%)	81,958 (14.8%)	62,443 (13.8%)	19,515 (19.2%)	<0.0001

Data are expressed as mean±SD, number (percentage), or median (interquartile range).

BMI: body mass index, CKD: chronic kidney disease, HbA1c: glycosylated hemoglobin A1c

gorical variables were compared with *t*-tests and chi-square tests, respectively. Survival curves were constructed with the Kaplan-Meier method and compared using log-rank tests. A Cox proportional hazard analysis was performed to determine independent predictors for AD-related deaths, and cardiovascular risk factors were entered into the multivariate analysis. Stepwise multivariate Cox proportional hazard analyses were also performed to examine whether or not CKD was associated with aortic aneurysm rupture deaths and aortic dissection deaths. Age, hypertension, smoking, and CKD were included in the stepwise multivariate analysis for aortic aneurysm rupture deaths, whereas age, hypertension, and CKD were included in the stepwise multivariate analysis for aortic dissection deaths. Receiver operating characteristics (ROC) curves for AD-related deaths were constructed and used as a measure of the predictive accuracy of CKD for AD-related deaths. We calculated the net reclassification index (NRI) and integrated discrimination index (IDI) to measure the quality of improvement for the correct reclassification by the addition of CKD to the multivariate model. Values of $p<0.05$ were considered statistically significant.

All statistical analyses were performed using the standard statistical program packages (JMP version 12, SAS Institute, Cary, USA; and R 3.0.2 with additional packages including Rcmdr, Epi, pROC, and PredictABEL).

Results

Baseline characteristics and the comparison of clinical characteristics between subjects with and without CKD

The subjects' baseline characteristics are shown in Table 1. There were 236,606 men and 317,836 women. HT, DM, and DL were identified in 327,379 (59%), 51,793 (9.3%), and 272,441 (49%), patients, respectively. The mean eGFR was 75.6 mL/min/1.73 m^2. Proteinuria and CKD were identified in 32,452 (5.9%) and 101,830 (18%) patients, respectively.

Subjects with CKD were older and more likely to be men; have HT, DM, or DL; be a current smoker; or be taking anti-hypertensive, anti-diabetic, or anti-DL drugs than those without it. In addition, subjects with CKD showed higher FBS and HbA1c levels than those without it (Table 1).

Baseline characteristics and the comparison of clinical characteristics among surviving subjects, subjects with aortic aneurysm rupture death, and those with aortic dissection death

Subjects with aortic aneurysm rupture death were older and more likely to be men; have HT, DL, proteinuria, reduced eGFR, and CKD; be a current smoked; or be taking anti-hypertensive drugs than surviving subjects. In addition, subjects with aortic aneurysm rupture death showed higher creatine levels and a lower eGFR than surviving subjects

Table 2. Baseline Clinical Characteristics of Surviving Subjects, Subjects with Aortic Aneurysm Rupture Death, and Those with Aortic Dissection Death.

Variables	Surviving subjects n=554,311	Aortic aneurysm rupture death n=41	Aortic dissection death n=90
Age	62.0±9.3	67.5±5.3*	65.6±6.6*
Male, n (%)	236,527 (43%)	30 (73%)	49 (54%)‡
BMI, kg/m^2	23.4±3.5	24.1±2.7	24.0±3.6
Hypertension, n (%)	327,269 (59%)	35 (85%)	75 (83%)‡
Diabetes mellitus, n (%)	51,783 (9.3%)	6 (14.6%)	4 (4.4%)
Dyslipidemia, n (%)	272,370 (49%)	28 (68%)	43 (47%)‡
Smoking, n (%)	84,198 (15%)	12 (29%)	17 (19%)‡
Biochemical data			
Creatinine (mg/dL)	0.72±0.40	0.94±0.37*	0.82±0.22
eGFR (mL/min/1.73m^2)	75.6±17.4	65.1±21.2*	67.7±17.9*
HbA1c (%)	5.4±0.7	5.5±0.5	5.3±0.5
Fasting blood sugar (mg/dL)	98±21	100±20	97±20
Proteinuria, n (%)	32,432 (5.9%)	9 (21.9%)	11 (12%)‡
Reduced eGFR, n (%)	78,9178 (14%)	20 (49%)	34 (38%)‡
CKD, n (%)	101,771 (18%)	20 (49%)	39 (43%)‡
Medications			
Anti-hypertensive drug, n (%)	165,980 (30%)	24 (59%)	45 (50%)‡
Anti-diabetic drug, n (%)	30,579 (5.5%)	3 (7.3%)	3 (3.3%)
Anti-dyslipidemia drug, n (%)	81,937 (14.8%)	11 (26.8%)	10 (11.1%)

Data are expressed as mean±SD, number (percentage), or median (interquartile range).
BMI: body mass index, CKD: chronic kidney disease, HbA1c: glycosylated hemoglobin A1c
*p<0.05 v.s. surviving subjects, †p<0.05 v.s. subjects with aortic aneurysm rupture, ‡p<0.05 by chi-square test.

(Table 2). In contrast, subjects with aortic dissection death were older and more likely to be men; have HT, proteinuria, a reduced eGFR, and CKD; be a current smoker; or be taking anti-hypertensive drugs than surviving subjects. In addition, subjects with aortic dissection death showed a lower eGFR than surviving subjects (Table 2).

CKD and AD-related deaths

All subjects were prospectively followed during the follow-up period of 2,123,512 person-years (median period of 4 years). During the follow-up period, there were 131 AD-related deaths, including 41 aortic aneurysm rupture deaths and 90 aortic dissection deaths. There were 59 and 72 AD-related deaths in subjects with and without CKD, respectively. A Kaplan-Meier analysis demonstrated that subjects with CKD had higher rate of AD-related death than those without it (Fig. 2).

To determine the risk factors for predicting AD-related death, we performed univariate and multivariate Cox proportional hazard regression analyses. In the univariate analysis, CKD was significantly associated with AD-related mortality (Table 3). Age, male sex, HT, and smoking were also associated with AD-related mortality. A multivariate Cox proportional hazard regression analysis showed that CKD was an independent predictor of future AD-related deaths after adjusting for age, sex, HT, DM, DL, and smoking (hazard ratio, 2.838; 95% confidence interval, 1.987-4.038; p<0.0001; Table 3).

To examine whether or not CKD was a common risk factor for aortic aneurysm rupture or aortic dissection death, we performed a multivariate analysis in a stepwise manner. The multivariate Cox proportional hazard regression analysis showed that CKD was significantly associated with aortic aneurysm rupture deaths after adjusting for age, HT and smoking (hazard ratio, 3.122; 95% confidence interval, 1.670-5.819; p=0.0005; Table 4). In addition, the multivariate Cox proportional hazard regression analysis demonstrated that CKD was significantly associated with aortic dissection death after adjusting for age and HT (hazard ratio, 2.874; 95% confidence interval, 1.872-4.378; p<0.0001; Table 4).

Improvement of reclassification by the addition of CKD to predict AD-related mortality

To examine whether or not the model fit and discrimination improved with the addition of CKD to the basic predictors, such as age, sex, HT, DM, DL, and smoking, we evaluated the improvement of the C index, NRI and IDI. The ROC curve analysis demonstrated that the C index of the baseline model was significantly improved by the addition of CKD (Fig. 3). The NRI and IDI were also significantly improved by the addition of CKD (Table 5).

Risk stratification

All subjects were divided into four groups based on a reduced eGFR (<60 mL/min/1.73 m^2) and the presence of pro-

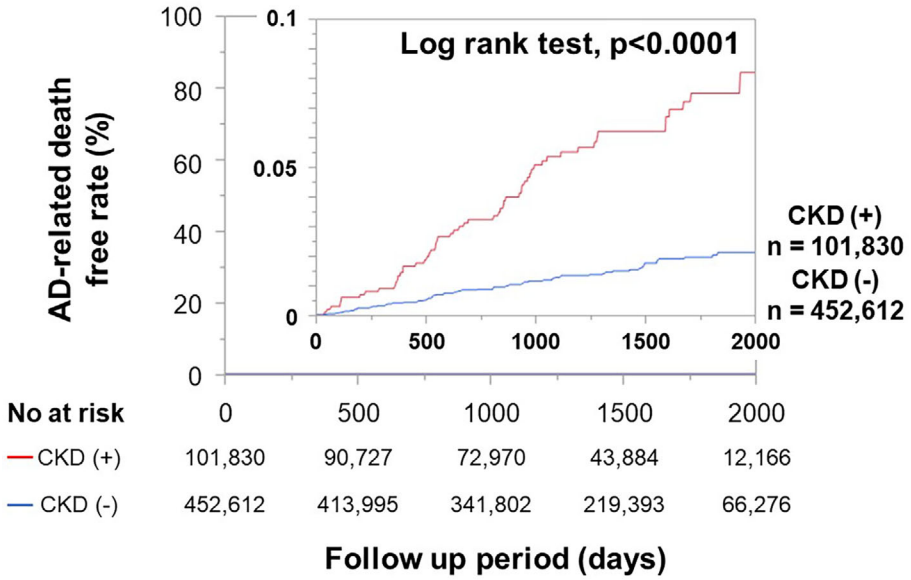

Figure 2. **A Kaplan-Meier analysis of aortic disease-related deaths for subjects with and without chronic kidney disease.**

Table 3. **Univariate and Multivariate Cox Proportional Hazard Analyses of Predicting AD-related Death.**

	Univariate analysis			*Multivariate analysis*		
Variables	HR	95%CI	p value	HR	95%CI	p value
Age	1.090	1.058-1.124	<0.0001	1.076	1.044-1.109	<0.0001
Sex	2.104	1.487-3.001	<0.0001	1.517	1.046-2.214	0.0281
Hypertension	3.783	2.425-6.199	<0.0001	2.794	1.779-4.606	<0.0001
Diabetes mellitus	0.814	0.400-1.470	0.5312	0.557	0.272-1.013	0.0555
Dyslipidemia	1.246	0.871-1.703	0.2505	1.076	0.761-1.527	0.6770
Smoking	1.617	1.051-2.408	0.0239	1.824	1.158-2.798	0.0104
Proteinuria	3.148	1.899-4.950	<0.0001			
Reduced eGFR	4.434	3.117-6.263	<0.0001			
CKD	3.855	2.724-5.433	<0.0001	2.838	1.987-4.038	<0.0001

AD: aortic artery disease, CI: confidence interval, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, HR: hazard ratio

Table 4. **Univariate and Multivariate Cox Proportional Hazard Regression Analyses of Predicting Aortic Aneurysm Rupture Deaths and Aortic Dissection Deaths.**

Variables	Aortic aneurysm rupture deaths			Aortic dissection deaths		
	HR	95%CI	p value	HR	95% CI	p value
Univariate analysis						
CKD	4.467	2.405-8.268	<0.0001	3.602	2.361-5.454	<0.0001
Multivariate analysis						
CKD	3.122*	1.670-5.819	0.0005	2.874#	1.872-4.378	<0.0001

CI: confidence interval, CKD: chronic kidney disease, HR: hazard ratio

*Multivariate model includes age, hypertension and smoking.

#Multivariate model includes age and hypertension.

teinuria. Fig. 4 shows the AD-related death per 100,000 person-years among the 4 groups. The highest mortality was observed in subjects with a reduced eGFR and proteinuria compared to other groups.

Discussion

The main findings in the present study were: (1) a Kaplan-Meier analysis showed that subjects with CKD had

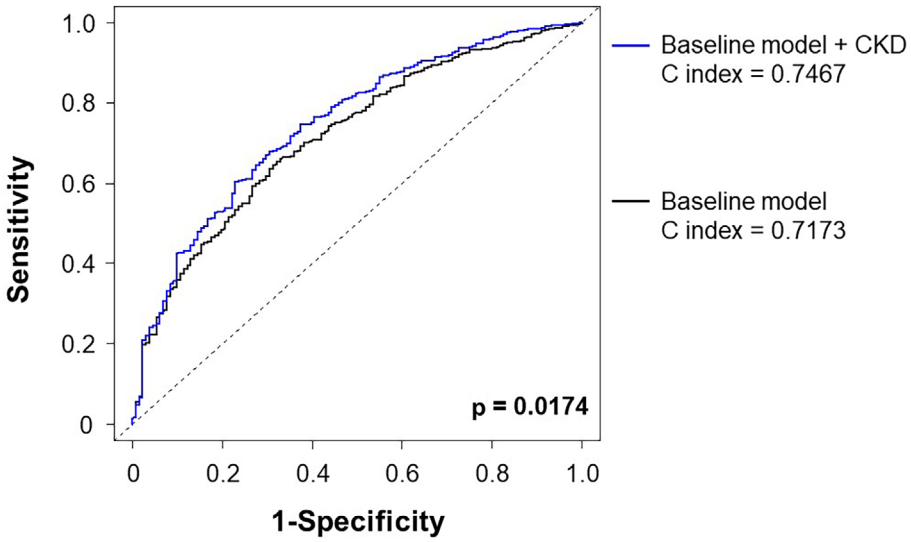

Figure 3. **A comparison of receiver operating characteristic curve analyses of the baseline model with and without chronic kidney disease.**

Table 5. **Statistics for Model Fit and Improvement with the Addition of CKD on the Prediction of AD-related Death.**

	NRI (95%CI, p value)	IDI (95%CI, p value)
Baseline model	Reference	Reference
+CKD	0.1094 (0.0029-0.2158, p=0.0252)	0.0001 (0.0001-0.0002, p<0.0001)

Baseline model includes age, sex, HT, DM, DL, and smoking.
CKD: chronic kidney disease, DM: diabetes mellitus, DL: dyslipidemia, HT: hypertension, IDI: integrated discrimination index, NRI: net reclassification index, 95%CI: 95% confidence interval

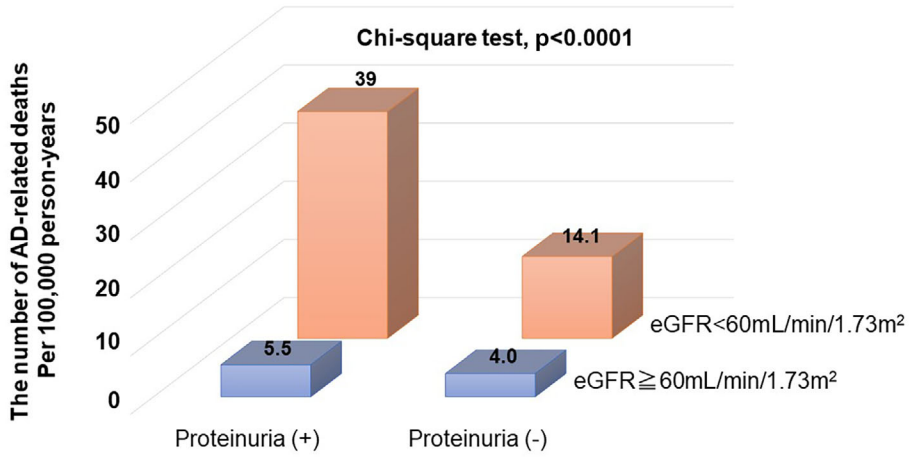

Figure 4. **The association of aortic disease-related death per 100,000 person-years with a reduced eGFR and proteinuria.**

higher rate of AD-related death; (2) a multivariate analysis showed that CKD was an independent predictor of AD-related death; (3) the addition of CKD improved the prediction of AD-related death in the general population; and (4) the combined assessment of a reduced eGFR and proteinuria stratified subjects at a high risk for AD-related death.

The major causes of AD development are considered to be atherosclerosis and connective tissue disease. However, the precise mechanism underlying AD development has not yet been fully elucidated. Recent advancements in basic and clinical AD research have clarified the important role of the renin-angiotensin-aldosterone system in the development of AD. Several experimental studies have indicated that angiotensin II and aldosterone receptor agonist initiate aneurysmal rupture and dissection in mice with medial degeneration (21-24). A clinical study indicated the beneficial effect

of renin-angiotensin-aldosterone system inhibitors on the development of AD, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (25, 26). CKD is closely associated with renin-angiotensin-aldosterone system activation in humans, since the kidney regulates renin secretion (27). Therefore, it was considered plausible for CKD to be associated with the development of AD through renin-angiotensin-aldosterone system activation. In addition, a recent report indicated that indoxyl-3-sulphate, a uremic toxin, was increased in patients with abdominal aortic aneurysm compared to clinical characteristic-matched subjects (28). Oxidative stress plays a causal role in the development of AD (29). Since uremic toxin induce reactive oxygen species in atherosclerotic lesions, CKD may contribute to AD development with resultant increases in oxidative stress. Further studies are needed to clarify the precise mechanism by which CKD worsens AD.

Pre-existing renal impairment was reported to be a risk factor for mortality after open surgery for type A aortic dissection (30, 31). Similarly, CKD was reported to be associated with increased morbidity and death after open abdominal aortic aneurysm repair or endovascular aortic repair (32). These reports indicated the importance of CKD in predicting the clinical outcome in patients with AD, even after surgical treatment. The ARIC study demonstrated that CKD is a risk factor for the aortic aneurysm in white and black subjects (17). We also showed that CKD was a novel risk factor for AD-related death, independent of cardiovascular risk factors, in an Asian general population. Notably, for the first time, we demonstrated that CKD is a risk factor for aortic dissection death in a general population.

A sub-analysis revealed that CKD was a common risk factor for aortic aneurysm rupture death and aortic dissection death. Of note, the C index, NRI, and IDI were all significantly improved by the addition of CKD, suggesting that CKD is an additional risk factor for confounding risk factors. Similar to cardiovascular disease, the combined assessment of the eGFR and proteinuria was able to risk-stratify subjects at a high risk for AD-related death. A reduced eGFR and proteinuria were reported to be associated with cardiovascular mortality (9). It was also reported that proteinuria, together with a reduced eGFR, was related to a high prevalence of HT (33), which is a risk for AD-related death (34). Hirayama et al. reported that the eGFR reduction was proportional to the increase in systolic blood pressure and that proteinuria promotes eGFR reduction in a Japanese general population (35). Therefore, it was plausible that the highest AD-related mortality in subjects with proteinuria and reduced eGFR resulted from worsening CKD.

The clinical perspective of the present study is that CKD at health checkups is a risk factor for AD-related death in the general Japanese population. Since CKD is an established risk factor for cardiovascular disease, screening for atherosclerotic disease is of critical importance for the management and risk stratification of subjects with CKD. However, little is known about the association of CKD with AD-related death. Screening elderly men with ultrasound is recommended to reduce the rate of death from abdominal aortic aneurysm rupture (36). Therefore, screening for aortic aneurysm and aortic dissection is also considered important in subjects with CKD.

Limitations

The strengths of the present study include its large sample size, prospective follow-up design, and nationwide data source. Therefore, our results are well generalized and highly reliable. However, there were some limitations as well. First, we assessed CKD at only one point. Since CKD develops with age, several subjects developed CKD during the follow-up period. Second, we did not examine AD development or medical data, such as surgical and endovascular aortic repair. Although AD can be fatal, some subjects survived, probably due to treatment. Thus, we underestimated the impact of CKD on the development of AD. Third, we have no information about the prevalence of AD. Fourth, we did not have enough data to analyze the impact of CKD on the aortic aneurysm rupture deaths or aortic dissection deaths by the site of aorta and type of dissection. Finally, we have no information on the details of medications used by this population.

Conclusion

AD was one of the major causes of sudden death, indicating the importance of primary prevention. This nationwide cohort revealed the effect of CKD on AD-related mortality in the general population. Similar to cardiovascular disease, the eGFR and proteinuria risk were able to stratify the subjects at a high risk for AD-related death in the general population. The results of the present study indicate that CKD is an additional risk factor for AD-related death among established risk factors in the general population and may be a target for the prevention and early identification of high-risk subjects for AD-related death in the general population.

All procedures performed in studies involving human participants were done so in accordance with the ethical institutional and/or national research committee at which the studies were conducted (Yamagata University, 2008) and in compliance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This study was performed according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted by the Ministry of Health, Labour and Welfare of Japan (http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000069410.pdf; http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf). In the context of the guideline, the investigators were not necessarily required to obtain informed consent, but we publicized information concerning this study on the web (http://www.fmu.ac.jp/univ/sangaku/data/koukai_2/2771.pdf) and ensured opportunities for the research subjects to refuse the use of their

personal information.

The authors state that they have no Conflict of Interest (COI).

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