Table 4. Metabolic syndrome and risk of kidney dysfunction: multivariate models[a]

	All subjects		Subjects without antihypertensive drug, diabetes, or CVD		Subjects ≤60 years without antihypertensive drug, diabetes, or CVD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Metabolic syndrome	2.12 (1.81–2.5)	<0.001	1.99 (1.56–2.54)	<0.001	2.11 (1.26–3.53)	0.005
Metabolic syndrome components						
Obesity	1.40 (1.21–1.62)	<0.001	1.21 (0.98–1.49)	0.08	1.56 (1.04–2.33)	0.03
Elevated blood pressure	1.95 (1.68–2.26)	<0.001	1.70 (1.41–2.04)	<0.001	1.53 (1.06–2.21)	0.02
Low HDL cholesterol	1.67 (1.42–1.97)	<0.001	1.42 (1.13–1.79)	0.003	1.78 (1.14–2.78)	0.01
Elevated triglycerides	1.72 (1.47–2.01)	<0.001	1.77 (1.43–2.2)	<0.001	1.86 (1.2–2.89)	0.005
Impaired glucose tolerance	1.55 (1.29–1.85)	<0.001	1.84 (1.42–2.38)	<0.001	1.94 (1.06–3.54)	0.03
Metabolic syndrome components, *N*						
0	1		1		1	
1	1.69 (1.38–2.06)	<0.001	1.48 (1.17–1.88)	0.001	1.60 (1.01–2.55)	0.046
2	2.34 (1.9–2.89)	<0.001	2.15 (1.66–2.77)	<0.001	2.27 (1.36–3.78)	0.002
≥3	3.49 (2.79–4.37)	<0.001	2.88 (2.14–3.87)	<0.001	3.09 (1.7–5.59)	<0.001
Trend across number of components	1.49 (1.39–1.59)	<0.001	1.43 (1.31–1.56)	<0.001	1.46 (1.22–1.74)	<0.001

Kidney dysfunction was defined by occurrence of estimated glomerular filtration rate <60 mL/min/1.73 m^2.
[a]Models were adjusted for sex and age.

Table 5. Metabolic syndrome and risk of proteinuria: multivariate models[a]

	All subjects		Subjects without antihypertensive drug, diabetes, or CVD		Subjects ≤60 years without antihypertensive drug, diabetes, or CVD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Metabolic syndrome	1.76 (1.57–1.98)	<0.001	1.64 (1.39–1.93)	<0.001	2.14 (1.69–2.7)	<0.001
Metabolic syndrome components						
Obesity	1.63 (1.48–1.79)	<0.001	1.6 (1.42–1.8)	<0.001	1.93 (1.62–2.31)	<0.001
Elevated blood pressure	1.59 (1.45–1.74)	<0.001	1.45 (1.3–1.61)	<0.001	1.61 (1.37–1.91)	<0.001
Low HDL cholesterol	1.19 (1.05–1.34)	0.006	1.22 (1.04–1.42)	0.01	1.3 (1.04–1.64)	0.02
Elevated triglycerides	1.28 (1.15–1.43)	<0.001	1.25 (1.08–1.44)	0.002	1.51 (1.23–1.85)	<0.001
Impaired glucose tolerance	1.73 (1.54–1.95)	<0.001	1.31 (1.16–1.48)	<0.001	1.49 (1.09–2.03)	0.01
Metabolic syndrome components, *N*						
0	1		1		1	
1	1.43 (1.27–1.61)	<0.001	1.29 (1.13–1.48)	<0.001	1.31 (1.07–1.61)	0.009
2	1.95 (1.72–2.21)	<0.001	1.73 (1.49–2.01)	<0.001	1.97 (1.57–2.48)	<0.001
≥3	2.46 (2.14–2.84)	<0.001	2.07 (1.72–2.49)	<0.001	2.75 (2.12–3.57)	<0.001
Trend across number of components	1.32 (1.27–1.37)	<0.001	1.27 (1.21–1.33)	<0.001	1.36 (1.27–1.47)	<0.001

[a]Models were adjusted for sex and age.

of kidney disease increased across a number of the fulfilled metabolic syndrome components. Furthermore, in our study including the largest number of subjects, all of the components of the metabolic syndrome were associated with increased risk of kidney disease even in subjects without hypertension or diabetes, although some components are not associated with kidney disease in prior studies [14,16–18]. Taken together, it is suggested that the pathogenesis of metabolic syndrome has an important role for kidney disease.

Chronic kidney disease is associated with inflammation and oxidative stress, even in patients with moderate kidney dysfunction [6,7,23], suggesting that persistent inflammation starts early in the process of kidney function decline. More severe kidney impairment is associated with a trend towards higher levels of inflammation, and inflammatory markers predict progression of kidney dysfunction [7,24]. Inflammation and oxidative stress also play an important role for pathology of the metabolic syndrome; all of the metabolic syndrome components are associated with inflammation and oxidative stress [25–27], levels of C-reactive protein and several antioxidants are high in the metabolic syndrome [8,9], and oxidized low-density lipoprotein is associated with incidence of the metabolic syndrome [28]. Therefore, the association between the metabolic syndrome and kidney disease may reflect activation of signaling pathways important for inflammation and oxidative stress, although inflammation markers such as C-reactive protein were not measured in this study population. Administration of anti-inflammatory drugs and antioxidant drugs (such as statins) may preserve kidney function and prevent proteinuria [29–31]. Because HRs of impaired glucose tolerance and dyslipidaemia for development of kidney dysfunction were relatively high in young- and middle-aged subjects without antihypertensive drug, diabetes,

or cardiovascular disease, modification of the deranged pathways underlying inflammation may be of more therapeutic value for preventing kidney disease in these subjects.

Since chronic kidney disease is generally progressive and irreversible, early therapeutic intervention to prevent development and progression of kidney dysfunction is important [5]. Diabetes and hypertension are the most common causes for end-stage kidney disease [5], and it is widely accepted that strict control of diabetes and hypertension is effective to prevent progression of chronic kidney disease [5,32,33]. Our data clearly showed that the metabolic syndrome is also an important therapeutic target to prevent development of chronic kidney disease even in young- and middle-aged subjects without hypertension, diabetes, or cardiovascular disease, who are generally considered at low risk [5].

Study limitations

The study population included more females than males. The medical history was self-reported. As waist circumferences were not available in our subjects, we used BMI to establish the diagnosis of obesity with adjustment to a Japanese population as a component of the metabolic syndrome [20]. Subjects who received antihyperlipidaemic drugs were excluded because of the lack of information about individual drug regimens. We used an estimated GFR instead of actual measurement [34–36], but this is a common approach in large population studies. Although treatment which modulates renin–angiotensin system including angiotensin converting enzyme inhibitors and angiotensin receptor blockers have beneficial effects on chronic kidney disease [5], we do not have information on individual drug regimens. However, the association of metabolic syndrome with kidney disease remained significant after the exclusion of subjects receiving antihypertensive drugs. It is controversial whether the increased risk of kidney disease in the metabolic syndrome is due to the syndrome as a whole or simply the sum of the risks of its individual component parts.

Conclusions

Physicians should be aware that subjects with the metabolic syndrome are at increased risk for the development of kidney disease, even in young and middle ages, and in the absence of major risk factors for chronic kidney disease. Derangement of biochemical indices associated with the metabolic syndrome may activate signaling pathways critical for the pathogenesis of kidney disease. Modulation of these signaling pathways may not only attenuate the risk of atherosclerotic cardiovascular disease but also reduce the risk of chronic kidney disease.

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Competing interests

None declared. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Five Year Study of Cardiovascular Risk Factors in Japanese People: Implications Concerning New Onset of Metabolic Syndrome

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Abstract

Background The incidence of metabolic syndrome (MetS) has not been fully studied.

Methods and Results The data of 35,534 subjects who underwent a health examination both in 1996 and 2001 were analyzed. Since the waist circumference was not available, modified criteria of MetS was used for those with 3 or more of the following items: 1) body mass index (BMI) $\geq$25 kg/m^2, 2) blood pressure $\geq$130 mm Hg in systolic and/or $\geq$85 mm Hg in diastolic, 3) triglycerides $\geq$150 mg/dL, 4) high-density lipoprotein (HDL) cholesterol $\leq$40 mg/dL in men, $\leq$50 mg/dL in women, and 5) fasting blood glucose (FBG) $\geq$ 100 mg/dL. The subjects who underwent therapy for hypertension, diabetes mellitus, and high TG were considered to have these items. The incidence of MetS over 5 years was determined and its risks were evaluated by Cox proportional-hazards models. During the follow-up of exactly 5 years, MetS developed in 2,853 (9.32%) among 30,623 subjects who had no MetS at baseline. The subjects who developed MetS were older, and had elevated BMI, blood pressure, TG and FBG ($p<0.001$ for all) and lower HDL ($p<0.034$ for men and $p<0.001$ for women). Each item of MetS and their combination was associated with a higher risk to develop MetS. Obesity (BMI $\geq$25 kg/m^2) alone or in combination with another item was associated with a higher risk to develop MetS suggesting it plays a key role.

Conclusion MetS using BMI developed in 9.32% over 5 years or 1.86%/year. Each item of MetS or their combination showed a high risk to develop MetS. Obesity was associated with a higher hazard ratio to develop MetS.

Key words: metabolic syndrome, incidence, general population

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Introduction

Metabolic syndrome (MetS) is characterized by a clustering of atherosclerotic risk factors, including obesity, hypertension, impaired glucose metabolism, and dyslipidemia and criteria have been proposed by several organizations (1-5). The components of MetS tend to cluster more frequently than to occur by chance (6). Of these, insulin resistance was initially believed to play a key role in MetS (7), but the roles of adipocytokines released from visceral adipose tissue have been increasingly emphasized (8, 9). In addition, both inflammation and oxidative stress have been implicated in the pathogenesis of MetS (10, 11). MetS is associated with development of diabetes mellitus (11, 12), kidney dysfunction (13), and cardiovascular diseases and increased mortality (14-17).

The prevalence of MetS has been reported by many studies (1, 6, 18) but, the incidence of MetS in the general population has not been well documented (19-22). In this study, we evaluated new onset of MetS in the Japanese population. However, we had to modify the criteria of MetS

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Table 1. Baseline Characteristics of Subjects with and without Metabolic Syndrome (MetS)

	All subjects (n=35,534)	Without MetS n=30,623	With MetS# n=4,911
Male (%)	32.1	32.2	32.1
Age (years)	59.4±10.0	59.1±10.0	61.7±9.0*
BMI(kg/m^2)	22.8±2.9	22.4±2.6	25.7±2.8*
Blood pressure (mmHg)			
systolic	128.7±17.3	126.9±16.9	140.5±14.9*
diastolic	77.4±10.7	76.4±10.5	83.3±9.8*
HDL cholesterol (mg/dL)			
Men	60.4±15.2	62.3±5.5	49.9±13.8*
Women	64.9±14.6	66.6±14.5	51.5±13.0*
Triglyceride(mg/dL)	100.8±65.8	90.1±48.0	167.7±108.6*
Fasting glucose(mg/dL)	93.2±14.0	91.7±12.1	102.9±19.7*
HbA1c(%)	5.13±1.01	5.07±0.97	5.43±1.11*

Values are expressed as mean±SD or the number when indicated. #: MetS according to NCEP-ATP-III.
*:$p<0.001$

since the waist circumference was not available at that time.

Methods

Study subjects

This community-based, observational cohort study was based on data of the annual health examinations at the Niigata Association for Comprehensive Promotion and Research Foundation (Niigata, Japan) (6, 18). This examination is supported by the local government and is available to residents over 20 years. The examination consists of a detailed medical history; physical examination, blood examination including blood cell count and biochemical markers, chest X-ray and a 12-lead ECG. This report included 35,534 subjects who underwent the examination both in 1996 as the baseline examination and 5 years later.

Definition of metabolic syndrome

Because of the lack of data of waist circumference, we diagnosed MetS when subjects had at least 3 of the following items: 1) elevated body mass index (BMI) (≥25 kg/m^2), 2) elevated systolic (≥130 mmHg) and/or diastolic blood pressure (≥85 mmHg), 3) elevated triglycerides (≥150 mg/dL), 4) low high-density lipoprotein (HDL) cholesterol (≤40 mg/dL in men, ≤50 mg/dL in women), and 5) elevated fasting blood glucose (FBG)≥100 mg/dL. The subjects who were under therapy for hypertension, diabetes mellitus, and high TG were considered to have these items.

BMI was calculated by dividing the weight in kilograms by the square of the height in meters and this was used in place of waist circumference which was not available in our database at that time. Because of the differences in BMI between Japanese and Western populations, values ≥25 kg/m^2 were considered elevated (in contrast to ≥30 kg/m^2 as in Western populations) according to criteria of the Japan Society for the Study of Obesity (23-25).

Data analysis

The baseline characteristics between the subjects who developed MetS over 5 years were compared with those who did not. Comparisons were undertaken by the unpaired t-test for continuous variables which were expressed as mean ± SD and the X^2 test for categorical variables. Hazard ratios and 95% CIs were calculated from Cox proportional-hazard models. Cox models were adjusted for age as a continuous value and for gender to evaluate the contribution of each component of MetS and their combinations in the baseline data. All statistical analyses were performed with SPSS, version 12.0 (SPSS Inc., Chicago, Ill).

Two-sided values of P at 0.05 were considered statistically significant. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and approved with the manuscript as written.

Results

Baseline characteristics of study subjects

Baseline characteristics of the 35,534 subjects in this study are shown in Table 1. The mean age was 59.4 ± 10.0 years, and 67.9% of the subjects were women. The prevalence of each item of MetS was 20.6%, 53.1%, 12.6%, 18.7% and 21.1% for obesity, elevated blood pressure, low HDL cholesterol, high TG, and abnormal glucose metabolism, respectively. Hypertension was present in 20% and an-

Table 2. Comparisons of Components of Metabolic Syndrome (MetS) between Subjects with and without New Onset MetS at Baseline and 5 Years Later

	Baseline(1996)		2001	
	Without MetS n=27,770	With New MetS n=2,853	Without MetS n=27,770	With New MetS n=2,853
Age (years)	58.9±10.2	61.0±9.3*		
Male sex (%)	32.4	30.4**		
BMI (kg/m²)	22.2±2.5	24.5±2.7*	22.2±2.6	25.2±2.9*
Blood pressure (mmHg)				
systolic	126.1±16.7	134.5±16.2*	127.5±17.3	140.0±15.0*
diastolic	76.1±10.4	80.5±10.1*	75.7±10.4	81.6±10.2*
HDL cholesterol (mg/dL)				
Men	62.8±15.5	56.6±15.2*	62.5±14.8	53.7±14.7*
Women	67.3±14.2	60.1±13.4*	67.4±13.9	57.5±14.3*
Triglyceride (mg/dL)	87.7±46.0	113.1±59.6*	87.4±44.2	140.0±84.6*
Fasting glucose (mg/dL)	91.3±11.9	95.7±13.1*	93.6±12.9	103.1±15.8*
HbA1c (%)	5.06±0.97	5.17±1.02*	5.06±0.50	5.32±0.60*

HbA1c was available from 60% of subjects. *:p<0.001. **:p<0.05.

tihypertensive treatment was given to 14.0%. Diabetes was found in 12% and 2.4% were under treatment. MetS was present in 4,911 subjects (13.8%).

Subjects with MetS were older (p<0.001). The subjects who had MetS at baseline had elevated BMI, blood pressure, TG and abnormal FBG and decreased HDL to a greater extent than those who did not (Table 1). HbA1c was measured only in 60% which was higher in MetS (Table 1).

New onset of metabolic syndrome

During the follow-up of exactly 5 years, MetS developed in 2,853 (9.32%) among 30,623 subjects without MetS at the baseline study. This translates into the incidence of MetS at 1.86%/year.

As shown in Table 2, the subjects with new onset of MetS after 5 years were older (p<0.001) and less likely to be male (p<0.034). BMI, blood pressure, TG and FBG were higher in the subjects with MetS compared to those 27,770 subjects without new MetS (≦0.001 for all), and HDL was lower in the former (p<0.034 for men and p<0.001 for women). Furthermore, in the subjects with newly developed MetS (n=2,853), BMI, blood pressure, TG, FBG and HbA1c increased and HDL decreased significantly over 5 years while those without MetS (n=27,770) showed no change (Table 2). The prevalence for 0, 1 and 2 items of MetS was 5.3%, 28.7% and 66.0% in those who developed MetS and 35.2%, 41.7% 23.1% in the those who did not and the former often had 2 or more factors of MetS (p<0.001).

The relationship between the incidence of MetS and age or gender is shown in Fig. 1. In all, the incidence of MetS was around 4.68% and 4.22% for the 3rd and 4th decade and increased after the 5th decade and reached its peak in the 7th and 8th decade: 10.84% and 10.93% respectively, and thereafter, it declined to 8.33%. While in females, the incidence was very low in the 3rd and 4th decade (<1.5%), it increased linearly to the 9th decade (Fig. 1).

Risks for new onset of metabolic syndrome

The hazard ratios for those at risk to develop MetS are shown in Table 3. Each item and their combinations were associated with increased hazard ratios compared to cases without any item of MetS. Of note, when obesity was present alone or in combination with another factor, the hazard ratio was higher in comparison with other items and combinations. The presence of two items was associated with a higher hazard ratio than a single item: 18.90 vs. 4.55, whereas the ratio was 1.0 for those who had no item (p< 0.001).

Discussion

The clustering of interrelated risk factors of MetS is closely associated with the development of diabetes mellitus (12, 20), kidney dysfunction (13) and atherosclerotic cardiovascular disease and this has a strong association with stroke, myocardial infarction and all-cause mortality (15-17). Furthermore, MetS is confirmed to be a risk factor for newly developed atrial fibrillation (18). To reduce morbidity and mortality from cardiovascular events, it is very important to prevent the new onset of MetS and manage it properly and the Japanese government has started comprehensive medical examinations in the community.

For the diagnosis of MetS, NCEP-ATP III proposed a set of criteria in 2001 which continue to be widely accepted (1) and in 2005, the AHA and NHLBI modified the criteria with a reduction in the threshold for impaired glucose intol-

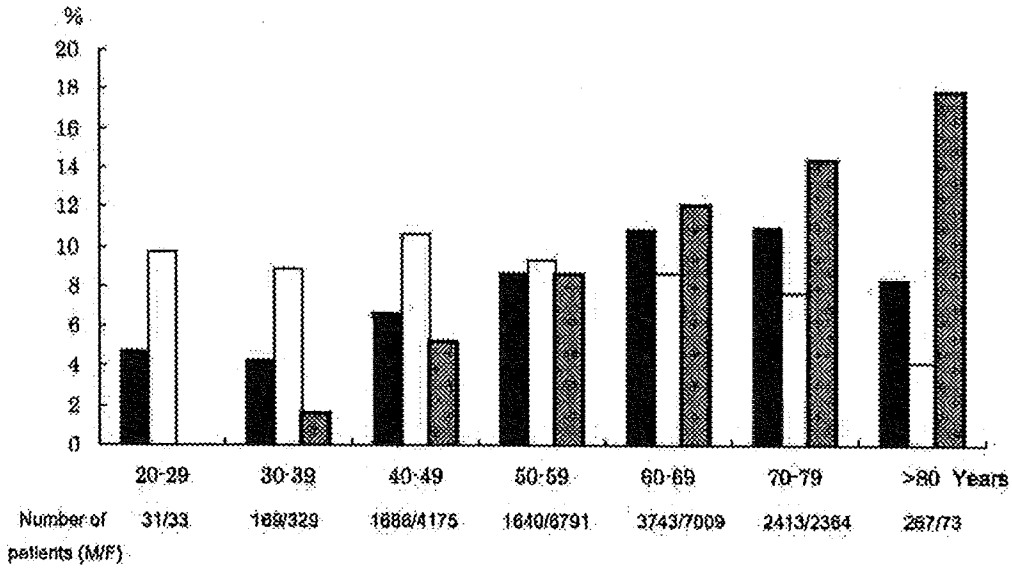

Figure 1. The relationship between the incidence of metabolic syndrome and age and gender. The number of subjects under 40 and those over 80 were relatively small. The overall incidence reached a peak around the 7th and 8th decade and then decreased. In females, the incidence increased as age advanced and was quite different from that of males. Black bar: all. White bar: male. Shadow bar: female.

Table 3. Multivariate Analysis with Development of Metabolic Syndrome as the Dependent Variable

Factor	HR (95% CI)	p value
MetS item		
Obesity	7.68(6.97-8.46)	<0.001
Elevated blood pressure	3.21(2.93-3.52)	<0.001
Low HDL cholesterol	4.56(4.01-5.20)	<0.001
Elevated triglycerides	4.41(3.96-4.91)	<0.001
Impaired glucose tolerance	3.35(3.01-3.72)	<0.001
Combination of Items of MetS		
High BMI+high BP	9.28(8.28-10.41)	<0.001
High BMI+low HDL	9.13(6.76-12.33)	<0.001
High BMI+high TG	12.10(9.40-15.57)	<0.001
High BMI+IFG	11.98(9.23-15.54)	<0.001
High BP+low HDL	7.37(6.08-8.94)	<0.001
High BP+high TG	5.51(4.47-6.35)	<0.001
High BP+IFG	3.89(3.43-4.41)	<0.001
Low HDL+high TG	6.32(4.94-8.09)	<0.001
Low HDL+IFG	6.04(4.04-9.03)	<0.001
High TG+IFG	6.62(4.90-8.94)	<0.001

Obesity (BMI≥25 kg/m^2) alone or in combination with another item was associated with higher risk.

erance, in order to optimize sensitivity and specificity for predicting future events and death (2). Additional criteria have been proposed for the diagnosis of MetS by some societies and countries, and the cut-off criteria or the waist circumference was modified (3, 4). The waist circumference has been used in most criteria but the American Association of Clinical Endocrinologist (AACE) is using BMI (≥25 kg/m^2) for the diagnosis of obesity (5). Depending on these criteria, the prevalence of MetS has been reported in many countries but the incidence of MetS has been poorly studied.

In the present community-based study, the baseline data showed MetS occurred in 13.8% of subjects. Of these, 9.32% of the 30,623 subjects who were non-MetS at baseline met the criteria of MetS 5 years later. Each item posed a risk to develop MetS and obesity (BMI ≥25 kg/m^2) was associated with a higher hazard ratio in developing MetS as

shown in Table 3.

We used BMI ($\geq$25 kg/m^2) as the criterion of obesity since the data of the waist circumference was not available at that time. So the prevalence or incidence of MetS of the current study might be an approximation of the MetS with diagnosis using the waist circumference (3, 4). However, using the same criteria, MetS as currently defined here, was a predictor of new onset atrial fibrillation which was associated with the clinical significance (18).

The incidence of MetS has been reported in few studies. In the Framingham study, multimarkers were evaluated to investigate the effects on the incidence of MetS (20). During the mean follow-up of 2.9 years, 282 of 1,473 participants without prevalent MetS at baseline developed MetS, the incidence was 6.60%/annualy or 66.0%/1,000 person-year (20). In another study, 75 of the 184 hypertensive patients (41%) initially free of MetS at baseline subsequently fulfilled the criteria for MetS during the 4 years of follow up (19). These two studies showed a higher incidence of MetS compared to that found in Japanese people in the present study. The precise reason for the difference in the incidence of MetS is not apparent, but racial and/or dietary habits may play a role. A higher calculated CHD risk ($p<0.001$) was found in those who developed MetS compared with those who did not (19).

Patients who developed MetS had higher baseline BMI, triglycerides and lower HDL cholesterol (19, 20). In the present study, all items and their combinations were associated with increased hazard ratios compared to cases without any item of MetS (Table 3). Of note, when obesity was present alone or in combination with another factor, the hazard ratio was higher in comparison with other items and combinations. Fox et al showed an association of both subcutaneous and visceral adipose tissue with an increased risk to develop MetS and the odds were stronger for an increase in visceral adipose tissue compared with that of subcutaneous adipose tissue (22). This finding suggests that visceral adipose tissue plays a more important role in the development of MetS and that waist circumference is a better indicator than BMI as employed in many criteria (1-4).

We had some limitations in this study. First, we used BMI since the waist circumference was not available at that time. As mentioned above, BMI will represent both visceral and cutaneous obesity but, visceral obesity is believed to play a more important role in MetS (22) and visceral obesity might be undetectable using BMI. The superiority of waist circumference to BMI might necessitate further study.

Another limitation is that the subjects were informed of the results of the examination and the subjects were recommended to correct abnormalities by changing dietary or exercise habits or having medical consultation or therapy. Such interventions might reduce the incidence of MetS. Furthermore, the presence of structural heart disease was determined by self-reporting, physical examination, electrocardiogram, and chest X-ray, but not by other methods such as echocardiography. The risk of developing a cardiovascular event was not determined in those with new onset MetS in the present study and further studies are necessary. However, with these limitations, it is apparent that BMI is a good predictor of accumulation of items of MetS.

In conclusion, after 5 years MetS developed in 2,853 (9.32%) among 30,623 subjects who were free from MetS at the baseline study. The presence of each item or their combination was associated with an increased risk for developing MD and obesity was associated with a higher hazard ratio in developing MetS.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Efficacy of Procainamide and Lidocaine in Terminating Sustained Monomorphic Ventricular Tachycardia

– Retrospective Case Series –

Satoru Komura, MD; Masaomi Chinushi, MD; Hiroshi Furushima, MD; Yukio Hosaka, MD; Daisuke Izumi, MD; Kenichi Iijima, MD; Hiroshi Watanabe, MD; Nobue Yagihara, MD; Yoshifusa Aizawa, MD

Background: The efficacy of antiarrhythmic drugs in terminating sustained monomorphic ventricular tachycardia (SMVT) was assessed in a retrospective manner to provide a basis for recommending their use.

Methods and Results: The 90 patients were included in this study to evaluate the efficacy to terminate SMVT using procainamide or lidocaine. All patients were alert and responsive. The mean systolic blood pressure was 91±25 mmHg (range, 40–150 mmHg). SMVT was diagnosed from ECG recordings and later in an electrophysiologic study. VTs with a cycle length of 329±55 and 324±61 ms were treated with the mean doses of 358±50 mg and 81±30 mg of procainamide and lidocaine and were terminated in 53/70 (75.7%) and in 7/20 (35.0%) respectively. The drugs were discontinued if there was no rise in blood pressure after slowing of the tachycardia rate or if there were signs of impending deterioration in consciousness. Though procainamide was effective, blood pressure was often low and DC shock should be available at all times during administration of the drug.

Conclusions: Procainamide, the relatively older drug, was more effective than lidocaine in terminating SMVT associated with structural heart diseases. This is a retrospective analysis but can form the basis for formulating guidelines for initial management of SMVT. (*Circ J* 2010; **74:** 864–869)

Key Words: Antiarrhythmic agents; Arrhythmia; Ventricular tachycardia

The association of ventricular tachyarrhythmia with sudden cardiac death can be seen from the results of electrophysiologic studies (EPS) wherein sustained ventricular tachyarrhythmia can be repeatedly induced.[1,2] In patients who die suddenly during recording of ambulatory ECG, approximately 80% are found have died from ventricular tachycardia (VT) or fibrillation (VF).[3,4]

VF requires immediate termination before arrival at hospital, and basic life support and advanced cardiovascular life support are essential for rescue.[5] Sustained monomorphic VT (SMVT) of a rapid rate requires prompt termination, but, occasionally, SMVT may show stable hemodynamics and in such cases antiarrhythmic drugs can be administered to terminate the arrhythmia.

Procainamide is recommended as the initial treatment[6] and is often effective for terminating SMVT.[7–9] On the other hand, lidocaine had been widely used to terminate VT but in several studies its efficacy seemed to be limited.[10–15] Lidocaine is now recommended as an alternative to amiodarone or for SMVT associated with acute myocardial ischemia or infarction.[6]

Recently, intravenous amiodarone became available in Japan and its indication for treatment of tachyarrhythmia seems to be expanding.[16] It is indicated for SMVT that is hemodynamically unstable, refractory to conversion with countershocks or recurrent despite procainamide or other agents, and comparative studies of the drugs are still necessary for correct management of SMVT.[5] In fact, the efficacy of amiodarone for terminating stable SMVT is relatively low.[17,18] Another class III drug, nifekalant, is indicated in Japan for refractory ventricular tachyarrhythmia,[19–21] and it is effective but associated with excessive QT prolongation and a risk of developing torsades de pointes.

We conducted a retrospective survey of the efficacy of procainamide in terminating SMVT and in the present study we discuss our results with those of previous studies.[7–15] The efficacy of lidocaine in SMVT cases experienced during the same time period was also investigated.

Methods

Patients

From the records of consecutive patients with SMVT ad-

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Table 1. Clinical Characteristics of the Patients Treated With Procainamide or Lidocaine

	Procainamide	Lidocaine	P value
Patients	70	20	–
M/F	50/20	13/7	NS
Mean age	57±26	61±12	NS
Underlying heart disease			
Previous MI	18	4	NS
IDCM	10	3	NS
HCM	4	1	NS
ARVC	9	3	NS
Cardiac sarcoidosis	5	2	NS
LV aneurysm	4	1	NS
Postcardiac surgery	4	2	NS
Miscellaneous	16	4	NS

MI, myocardial infarction; IDCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular dysplasia; LV aneurysm, arrhythmogenic left ventricular aneurysm of unknown cause.

Table 2. Echo- and Electrocardiographic Characteristics of the Patients Treated With Procainamide or Lidocaine

	Procainamide (n=70)	Lidocaine (n=20)	P value
LA dimension	42±8	40±8	NS
LV diastolic dimension	54±10	54±8	NS
LV ejection fraction	50±16	46±15	NS
SMVT			
Cycle length (ms)	329±55	324±61	NS
Morphology (LBBB/RBBB)	32/38	8/12	–

LV, left ventricle; SMVT, sustained monomorphic ventricular tachycardia; LBBB/RBBB, left bundle branch block/right bundle branch block.

mitted to Niigata University Hospital in the past 10 years, 90 patients were included in the present study. All patients had SMVT with clear consciousness on admission and were treated either with procainamide or lidocaine as the initial therapy. The male to female ratio was 67:23 and the mean age was 60±16 years.

As underlying heart diseases, previous myocardial infarction was found in 22 patients, idiopathic dilated cardiomyopathy in 13, hypertrophic cardiomyopathy in 5, arrhythmogenic right ventricular dysplasia in 12, cardiac sarcoidosis in 7, an arrhythmogenic left ventricular aneurysm in 5, postcardiac surgery for tetralogy of Fallot or double-outlet right ventricle in 6, and miscellaneous with concomitant diseases including chronic lung diseases, diabetes mellitus, systemic hypertension or unknown causes in the remaining 20 patients.

Diagnosis of SMVT

VT was diagnosed from the ECG recordings: (1) wide regular tachycardia (>100 beats/min), (2) P-QRS dissociation, and (3) fusion complexes between the basic QRS morphology and that of VT. SMVT showed a uniform QRS morphology in 12-lead ECG during tachycardia lasting more than 30 s. Actually, SMVT lasted more than 30 min after the onset of tachycardia in all because it developed out of the hospital and patients were then transferred to hospital.

All patients underwent EPS after admission and SMVT was confirmed from the induced tachycardia, which showed a QRS morphology identical to that of the clinical VT.[18,19]

Drug Administration

Before the administration of drugs, it was confirmed that the patients were alert and responsive and that the delivery of DC shock was available if required. Procainamide is the first-line drug used by us to terminate stable SMVT and it is given intravenously at 100 mg over 1–2 min. The endpoint was termination of tachycardia, drug-induced hemodynamic deterioration, or completion of the maximal dosage (800 mg). When procainamide resulted in no slowing of the tachycardia rate at a dose >400 mg, its administration was ceased.

Lidocaine was administered as a bolus of 50 mg and repeated while SMVT lasted and its selection was determined by physician's choice. The endpoint was either termination of tachycardia or the dosage reaching 150 mg.[6,16]

Both drugs were terminated when physicians observed no slowing of the tachycardia rate or a tendency of acceleration or signs of deteriorating consciousness. The 2 drugs were singly administered in a drip after termination of VT if needed.

Exclusion Criteria

Patients with acute chest pain, suggestive of acute myocardial infarction or angina pectoris, were excluded from the analysis. Acute myocardial ischemia on the ECG was also excluded after termination of SMVT. Subsequent coronary angiography was used to classify the underlying heart diseases as ischemic or non-ischemic.

Those who required DC shocks for unstable VT resulting in deterioration of consciousness or those who received pharmacological therapy or electrical intervention at another hospital before administration were also excluded, as were cases of spontaneous termination of SMVT before arrival at hospital. Patients who had no demonstrable heart disease and whose SMVT showed a right bundle branch block (RBBB) pattern with superior axis and were responsive to verapamil were also excluded from the present study.

Data Analysis

The clinical profiles of the 2 groups treated with procainamide or lidocaine were compared. The response of the cycle length (CL) of SMVT to the drug just prior to termination was determined, as well as the efficacy in terminating SMVT.

The clinical data and the dosages of the drugs were compared between the responders and nonresponders without termination of SMVT by either drug. In the procainamide-treated group, the cumulative efficacy of termination of tachycardia was plotted against the increments of dosage.

The numerical data are presented as mean±SD and comparisons between the 2 groups were made using the non-paired t-test. The prevalence or incidence was compared using the chi-square test. A P-value <0.05 was considered significant.

The protocol of the study was approved by the Ethics Committee of Niigata University School of Medicine.

Results

Clinical Characteristics

Previous myocardial infarction was found in 18/70 (25.7%) and 4/20 (20.0%) in the procainamide and lidocaine groups, respectively. Dilated or hypertrophic cardiomyopathy, arrhythmogenic right ventricular disease, and cardiac sarcoidosis were similarly found in both groups. Other heart diseases

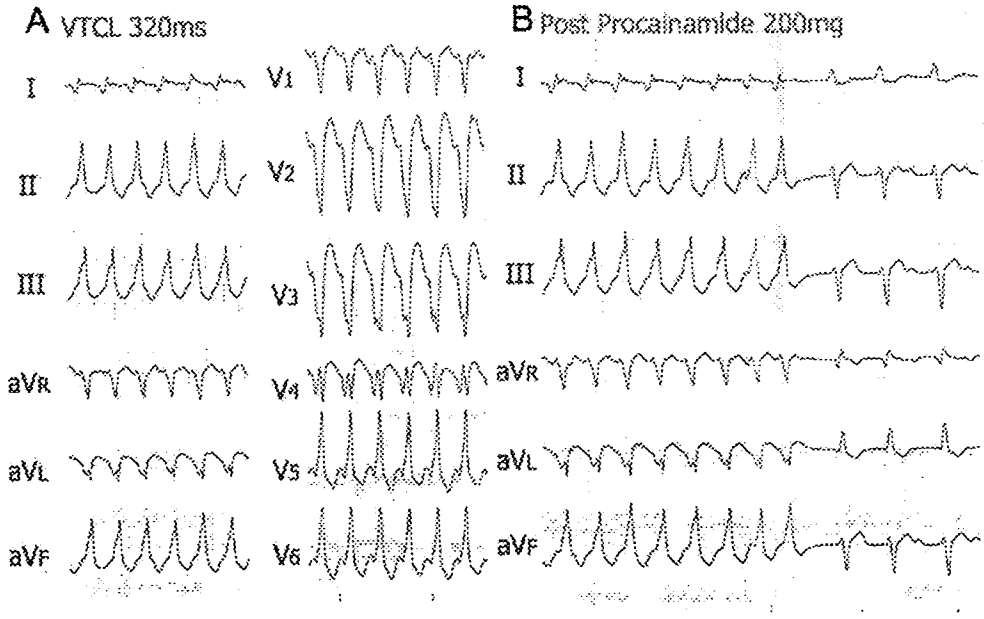

Figure 1. Termination of sustained monomorphic ventricular tachycardia (SMVT) by procainamide in a 56-year-old male, who developed palpitation and weakness and whose admission ECG showed SMVT. He was responsive and his blood pressure was 94/60mmHg. The tachycardia cycle length (CL) was prolonged from 320ms to 360ms and ventricular tachycardia (VT) was terminated at 200mg, a relatively low dose (see text and **Figure 2**).

included arrhythmogenic left ventricular aneurysm unrelated to coronary heart disease and postoperative cases of tetralogy of Fallot or double-outlet right ventricle. SMVT of undetermined causes were also found in both groups (**Table 1**).

ECG after termination of SMVT showed sinus rhythm in all except 2 patients with atrial fibrillation and 1 with a pacemaker for atrioventricular block. Echocardiographic study was performed after admission and the left atrial dimension, end-diastolic dimension of the left ventricle and the ejection fraction did not differ between the groups treated with procainamide and lidocaine: 42±8mm vs 40±8mm for the left atrial dimension, 54±10mm vs 54±8mm for the left ventricular dimension and 50±16% vs 46±15% for the ejection fraction, respectively.

All patients were alert and responsive. Systolic blood pressure was 91±25mmHg (range 40–150mmHg). The CL of VT before drug administration was similar in both groups: 329±55 vs 324±61ms for the procainamide- and lidocaine-treated groups, respectively (**Table 2**). The QRS morphology was RBBB/LBBB in 32/38 in the procainamide group and RBBB/LBBB in 8/12 in the lidocaine group.

Drug Efficacy

The mean doses were 358±50mg for procainamide and 81±30mg for lidocaine, and VT was terminated in 53/70 (75.7%) with procainamide (**Figure 1**) and 7/20 (35.0%) with lidocaine. Just prior to termination, the CL of SMVT was significantly prolonged with procainamide to 399±63ms ($P<0.001$) but not with lidocaine to 333±55ms (NS). The prolongation of the CL was greater with procainamide (19% on average) than with lidocaine (3% on average) ($P<0.05$). Of the cases of successful termination, SMVT was terminated in 80% with procainamide at <400mg and an additional 20% at 800mg (**Figure 2**). In 4 nonresponders to lidocaine, procainamide was given and terminated SMVT in 3. In 3 nonresponders to procainamide, lidocaine (2) or mexiletine (1) was given, but SMVT was terminated in only 1. DC shock was used in 16 nonresponders (22.9%) to procainamide and 10 nonresponders (50%) to lidocaine.

The QRS duration was prolonged with procainamide but not with lidocaine: 118±39ms vs 93±17ms ($P=0.066$) and the QTc intervals were 498±66 or 469±48$ms^{1/2}$ when VT was terminated by procainamide or lidocaine, respectively. Blood pressure was 118±23mmHg (systolic) and 73±14mmHg (diastolic) when SMVT was terminated and heart rate was 67±13 beats/min.

Comparison of Responders and Nonresponders

In the responders to procainamide, SMVT was terminated at a mean dose of 346±190mg and those without termination received a higher dose of procainamide: 580±264mg ($P=0.014$). There were no differences between the responders and nonresponders to procainamide in the echocardiographic or other characteristics of SMVT.

In the responders to lidocaine, SMVT was terminated at a mean dose of 68±30mg and those without termination received 82±28mg ($P=0.46$). Again, there were no differences in the echocardiographic or other characteristics of SMVT between the responders and nonresponders.

If blood pressure was stable or rose upon slowing of the tachycardia rate by the drugs, higher doses were administered. However, the drugs were discontinued before reaching the maximal doses in cases of low blood pressure or signs of a deterioration in consciousness.

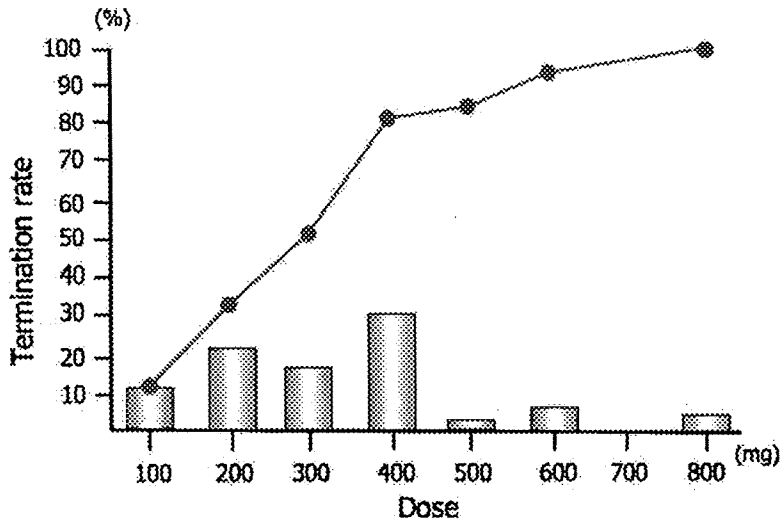

Figure 2. Cumulative rate of termination of ventricular tachycardia and the doses of procainamide. Of the cases of successful termination, ventricular tachycardia was terminated in 80% with procainamide at <400mg and an additional 20% at 800mg.

Adverse Effects

The QRS duration was wider in the procainamide group compared with the lidocaine group: 118±38ms vs 93±17ms (P=0.066) when tachycardia was terminated by either drug.

When hemodynamics remained unstable or there was signs of deterioration in consciousness, the drug was discontinued and the patients underwent electrical cardioversion. No major side-effects were observed in any patient.

Discussion

In the present study, procainamide terminated 75.7% of SMVT whereas lidocaine was effective in only 35.0%. There were no differences between the 2 treatment groups in the underlying heart diseases or in the ejection fraction of the left ventricle. The results seem compatible with those reported earlier[8–15] and summarized in **Table 3**, and could form the basis for recommending procainamide as the initial treatment of stable SMVT.[6,16]

Since an early report by Wellens et al,[7] many electrophysiologists have used procainamide to terminate SMVT and EPS-guided selection of antiarrhythmic drugs also suggests procainamide.[22] This drug might facilitate the induction of SMVT that is non-inducible in the baseline EPS.[22,23] Accordingly, we have been using procainamide as the drug of first choice in terminating SMVT since we started performing EPS.[23,24]

On the other hand, lidocaine also has some benefits: it is easy to administer and works rapidly,[25] and it has been previously recommended as the drug of first choice to terminate VT.[26] It is still recommended even now by some workers.[25] However, comparative studies have shown that procainamide is superior to lidocaine in terminating SMVT and in the present study procainamide was effective in 75.7% of cases while the efficacy of lidocaine was only 35.0% (**Table 3**).

The mechanism in most cases of SMVT is considered to be reentry, as suggested by the ability to induce or terminate tachycardia by programmed electrical stimulation.[23,24] Demonstration of the phenomenon of transient entrainment is another strong piece of evidence of a reentrant mechanism.[22,23,27,28] SMVT is usually unrelated to acute myocardial ischemia, but arises when there is scarring and residual myocardial tissue

Table 3. Efficacy of Procainamide and Lidocaine for Terminating Sustained Monomorphic Ventricular Tachycardia

Author	Year	No. of patients	Termination rate
Procainamide			
Wellens	1977	12	83%
Callan	1992	15	93%
Gorgels*	1996	15	80%
Present study	2009	70	76%
Total		112	80%
Lidocaine			
Armengol	1989	20	19%
Griffith	1990	24	30%
Ho*	1994	33	18%
Somberg*	2002	11	27%
Marill	1997	35	29%
Present study	2009	20	35%
Total		143	26%

*Randomized control study. The others are retrospective case series.

in which the myocardial cells are normally repolarized.[29] Endocardial mapping may show fractionated or continuous electrograms at the site of origin of SMVT,[30] and at the critical site, some cases of SMVT can be successfully ablated.[31]

Class I antiarrhythmic drugs preferentially depress the conduction within the area of slow conduction,[32–34] and procainamide is considered to result in termination by increasing the refractoriness within that area.[35,36] Caution needs to be paid to a fall in blood pressure when procainamide is given to patients with cardiac dysfunction.[37] Furthermore, long-term use of procainmide is limited because of its lower efficacy in preventing recurrence of SMVT and its adverse extra-cardiac effects.[38]

The efficacy of lidocaine in terminating SMVT is limited and though rarely, it can cause hemodynamic deterioration.[11,12,25] It is effective for tachyarrhythmia arising from ischemic myocardium because it binds preferentially to de-

pressed fast channels[23,27] and is effective in preventing VF in acute myocardial infarction.[39] However, lidocaine might cause an acceleration of the tachycardia rate.[22] Based on these findings, lidocaine is indicated as the second-line drug in recent guidelines.[5,6,16]

In Japan, intravenous amiodarone has become available and is the first-line drug for unstable or refractory VT.[16,40] Its efficacy for terminating stable SMVT has been reported as approximately 20–67%.[14,17,18] Nifekarant, another class III drug, is indicated for refractory or unstable VT[16,19–21] and is associated with prolongation of the QT interval.

Study Limitations

This was a retrospective study of a relatively small number of cases of SMVT. However, previous studies, mainly from foreign countries, also involved a limited number of patients and their results were comparable to ours and are evidence for the correct drug choices in the initial management of SMVT.

The study was not randomized and involved a small number of cases in the lidocaine-treated group because we have been using procainamide as the first-line therapy to terminate SMVT since we started performing EPS. Procainamide has been used in most SMVT cases, but some cardiologists, especially younger doctors, tend to choose lidocaine, depending on their knowledge of the literature. Because the use of lidocaine was related to physician preference, its low efficacy in terminating SMVT might not be related to the bias in patient selection.

Finally, the maximal doses of either drug were rarely given, because although the patients were alert and responsive, blood pressure was often very low. If there was no slowing of the tachycardia rate and a rise in blood pressure, or impending deterioration in consciousness was suggested, drug administration was stopped and the patients were prepared for DC cardioversion under general anesthesia.

In conclusion, procainamide, a relatively older drug, is effective in terminating SMVT associated with structural heart diseases and can be the drug of first choice. The efficacy of lidocaine was low and its use seems to be limited.

Disclosure

Conflict of Interest: none to declare.

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Close bidirectional relationship between chronic kidney disease and atrial fibrillation: The Niigata preventive medicine study

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Background Atrial fibrillation (AF) and chronic kidney disease share risk factors and pathophysiologic mechanisms, suggesting that two conditions have close relationships.

Methods This is a prospective community-based observational cohort study including 235,818 subjects based upon a voluntary annual health check-up program in Japan. We studied the association of kidney dysfunction at entry with subsequent new-onset AF and the association of AF at entry with the development of kidney disease.

Results During a follow-up of 5.9 ± 2.4 years, AF developed in 2947 subjects (1.3%). Baseline serum creatinine and estimated glomerular filtration rate (GFR) were associated with risk of subsequent AF. The HRs (95% CI) for AF were 1.32 (1.08-1.62) and 1.57 (0.89-2.77) for GFR 30 to 59 and <30 mL/min per 1.73 m^2, respectively. The effect of kidney disease on risk of new-onset AF remained significant in subjects without treated hypertension or diabetes. During the follow-up, 7791 subjects (3.3%) developed kidney dysfunction (GFR <60 mL/min per 1.73 m^2), and 11 307 subjects (4.9%) developed proteinuria. Atrial fibrillation at entry was associated with development of kidney dysfunction (HRs [95% CI], 1.77 [1.50-2.10]) and proteinuria (HR [95% CI], 2.20 [1.92-2.52]). The association persisted in subjects without treated hypertension or diabetes.

Conclusions Kidney dysfunction increased the risk of new onset of AF, and AF increased the risk of development of kidney disease. This finding supports the concept that the two conditions share common abnormal molecular signaling pathways contributing to their pathogenesis. (Am Heart J 2009;158:629-36.)

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice with a lifetime risk of 1 in 6 for subjects ≥40 years, even in the absence of antecedent congestive heart failure or myocardial infarction.[1,2] Atrial fibrillation is associated with an increased risk of ischemic stroke, heart failure, and death from any cause.[3-5] The number of patients with AF is increasing with a rise in the elderly population and increasing prevalence of chronic heart disease.[6,7] The public health problem of chronic kidney disease is also increasing in prevalence.[8,9] A significant bidirectional association has been described between chronic kidney disease and cardiovascular disease; chronic kidney disease is an independent risk factor for cardiovascular disease and cardiovascular disease is a risk factor for chronic kidney disease.[10,11] Recent evidence similarly suggests that there are close relationships between AF and chronic kidney disease,[12-16] although this has not been systematically studied in a large general population.

Multiple risk factors have been identified for the development of AF and for chronic kidney disease, and many are shared, notably, obesity, hypertension, type 2 diabetes, cardiovascular disease, and the metabolic syndrome, suggesting common underlying pathogenic mechanisms.[17-23] Furthermore, even moderate kidney dysfunction is associated with persistent inflammation and oxidant stress, factors that have also been implicated in the pathogenesis of AF.[24-27] Activation of the renin-angiotensin-aldosterone system has been invoked in the pathogenesis of kidney disease and of AF.[28-35] It has been also reported that electrocardiographic abnormalities (prolonged PR and QT intervals) are common in chronic kidney disease,[36] raising the possibility that kidney

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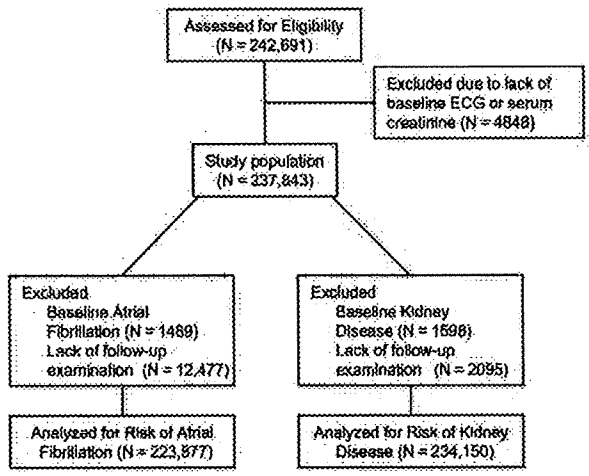
Figure 1



Subject flow though the analysis.

insufficiency can result in cardiac remodeling and AF. In this study, we tested the hypothesis that there are close bidirectional relationships between AF and kidney disease.

Methods

Study subjects

This community-based, observational cohort study was based on a program of voluntary annual health examinations in the Niigata Association for Comprehensive Health Promotion and Research, Niigata, Japan.[19] In the prefecture, annual health examinations supported by administration are available to residents ≥20 years of age. The population of the prefecture is about 2 400 000, and about 250 000 residents (~50% of subjects) receive the examination during one year. The annual examination consists of a detailed medical history, physical examination, blood examination including blood cell count and biochemical markers, urine tests, chest x-ray, and a 12-lead electrocardiogram (ECG). Urine protein level is measured using semiquantitative urine sticks (1+, 2+, and 3+ corresponding to protein levels of about ≥30, ≥100, and ≥300 mg/dL, respectively). The present report includes subjects who had at least one examination including ECG, serum creatinine, and urine protein level between 1996 and 1998 (designated the baseline examination) and received at least 1 successive annual examination after the baseline examination through 2005 (Figure 1).

Study outcomes

We studied the association between AF and kidney disease from both directions, namely evaluating (1) baseline kidney disease as a risk factor for subsequent AF and (2) baseline AF as a risk factor for subsequent kidney disease. The end points of this study were (1) development of AF, kidney dysfunction, or proteinuria for each analysis and (2) discontinuation of successive annual examinations. To study the association of baseline kidney dysfunction with the development of AF,

Table I. Baseline characteristics, according to estimated GFR at entry

	Estimated GFR (mL/min per 1.73 m²) at Baseline		
	≥60 (n = 219,725)	30-59 (n = 3,751)	<30 (n = 401)
Age, y	60.7 ± 11.7	71.1 ± 8.2†	69.6 ± 9.6†
Female sex , n (%)	149 484 (68)	2600 (69)	238 (59)†,§
Body mass index, kg/m²	22.9 ± 3.1	23.4 ± 3.2†	23.3 ± 3.2*
Blood pressure, mmHg			
Systolic	129.7 ± 17.8	135.5 ± 18.3†	142.1 ± 20.5†,§
Diastolic	75.6 ± 10.9	76.3 ± 11.6†	79.2 ± 12.9†,§
Serum creatinine, mg/Dl			
Men	0.8 ± 0.1	1.3 ± 0.1†	2.1 ± 1.7†,§
Women	0.6 ± 0.1	1.0 ± 0.1†	2.1 ± 4.0†,§
Estimated GFR, mL/min per 1.73 m²			
Men	100.8 ± 22.3	52.4 ± 5.7†	20.3 ± 10.5†,§
Women	104.8 ± 25.1	54.6 ± 5.3†	22.6 ± 14.5†,§
Antihypertensive drug, n (%)	41,694 (19)	1,595 (43)†	240 (60)†,§
Diabetes, n (%)	13,012 (6)	294 (8)†	50 (12)†,‡

* $P < .05$ versus GFR ≥60 mL/min per 1.73 m².
† $P < 0.001$ versus GFR ≥60 mL/min per 1.73 m².
‡ $P < .01$ versus GFR 30-59 mL/min per 1.73 m².
§ $P < .001$ versus GFR 30-59 mL/min per 1.73 m².

Table II. Incidence of AF by GFR categories

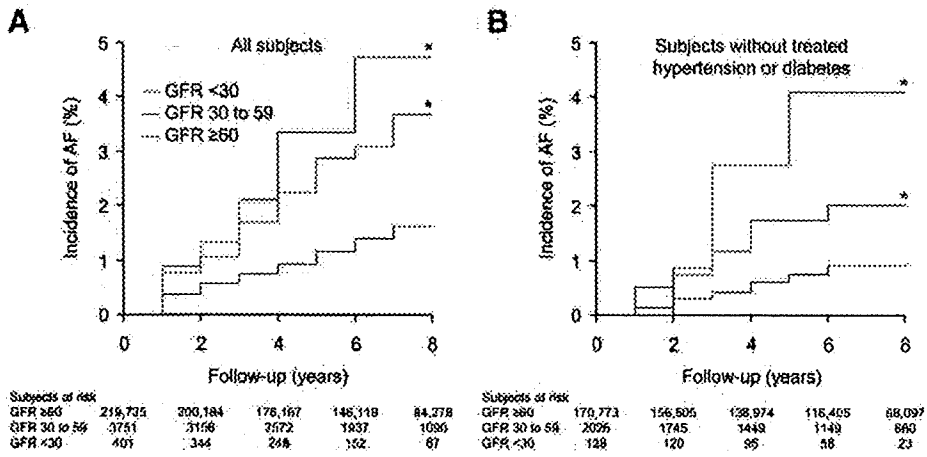
	GFR at baseline, mL/min per 1.73 m²		
	≥60	30-59	<30
Age-adjusted Incidence	2.2 (2.1-2.3)	5.1 (4.1-6.1)	6.6 (2.9-10.3)

Values are incidence per 1000 person-years (95% CI).

subjects who had a baseline examination that included ECG and serum creatinine level and had at least one consecutive annual follow-up ECG were included. Subjects who had a history of AF or atrial flutter or were in AF at the time of examination were excluded. The development of AF was diagnosed from the ECG recorded at a follow-up visit. Estimated glomerular filtration rate (GFR, mL/min per 1.73 m²) in each subject was calculated by the MDRD Study equation modified for Japanese population: $0.881 \times 186 \times \text{age}^{-0.203} \times \text{serum creatinine}^{-1.154}$ (if female × 0.742).[37]

To study the association of baseline AF with the development of kidney dysfunction and proteinuria, subjects were included if they had a baseline examination including ECG, serum creatinine, and urine protein levels and had at least one consecutive annual follow-up examination including serum creatinine and urine protein evaluations. Subjects who had baseline kidney dysfunction (GFR <60 mL/min per 1.73 m²) and/or proteinuria (urine stick result ≥1+) were excluded.[11] The development of kidney dysfunction was defined by a baseline normal value (≥60 mL/min per 1.73 m²) and a decline by ≥10 mL/min per 1.73 m², above the normal age-related

Figure 2



Cumulative risk of developing AF by baseline estimated GFR. Incidence of AF increased as baseline GFR decreased in all subjects (**A**) and in subjects without treated hypertension and diabetes (**B**). * $P < .001$ versus GFR ≥60 mL/min per 1.73 m^2.

decrease over 10 years,[23] to <60 mL/min per 1.73 m^2. Proteinuria was defined as a urine stick result ≥1+.[38]

Data analysis

Differences in baseline characteristics between groups were determined by Student t test or analysis of variance for continuous variables and by the χ^2 test for categorical variables. HR and 95% CIs were calculated from Cox proportional hazards models. Cox models were adjusted for age, sex, body mass index, systolic and diastolic blood pressure, treated hypertension, and diabetes in all subjects and were adjusted for age, sex, body mass index, and systolic and diastolic blood pressure in subjects without treated hypertension or diabetes. Disease incidence was estimated by the Kaplan-Meier method, and differences in the incidence among groups were determined by the log-rank test. All statistical analyses were performed with SPSS, version 12.0 (SPSS Inc, Chicago, IL). A 2-sided $P < .05$ was considered statistically significant. Values are expressed as mean ± SD.

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Results

Association of kidney disease with development of AF

The entire cohort, which was analyzed for the association of kidney disease with development of AF, included 223,877 subjects after elimination of the subjects with exclusions (Figure 1). The mean age was 60.9 ± 11.7 years and 68% of subjects were women (Table I). The mean serum creatinine was 0.6 ± 0.2 mg/dL at the baseline and the mean estimated GFR was 102.6 ± 25.1 mL/min per 1.73 m^2. Subjects with baseline GFR 30-59 mL/min per 1.73 m^2 and GFR <30 mL/min per 1.73 m^2 were identified in 1.7% and 0.2% of the study cohort, respectively. Subjects with GFR 30 to 59 or <30 mL/min per 1.73 m^2 were older than those with GFR ≥60 mL/min per 1.73 m^2, and there were more males in subjects with GFR <30 mL/min per 1.73 m^2 than those with GFR ≥60 or 30-59 mL/min per 1.73 m^2. Systolic and diastolic blood pressure increased with the severity of kidney dysfunction. The prevalence of treated hypertension or diabetes was higher in each group with a decreased GFR than that without.

During a mean follow-up of 5.9 ± 2.4 years corresponding to 1 034 756 person-years (5.2 ± 2.6 years [median 6 years] and 5.9 ± 2.4 years [median 6 years] in subjects with and without baseline kidney dysfunction, respectively), AF developed in 2947 subjects (1.3%), and the incidence of AF was 2.2 per 1000 person-years in all subjects. The incidence of AF was higher in subjects with baseline GFR <60 mL/min per 1.73 m^2 (5.2 per 1000 person-years) than those without (2.2 per 1000 person-years). The incidence of AF increased as baseline GFR declined (Table II). In univariate Cox models, increasing age, male gender, body mass index, systolic and diastolic blood pressure, treated hypertension, diabetes, and the estimated GFR were associated with new onset of AF. In multivariate models, the estimated GFR and all of other

Table III. Kidney dysfunction and risk of incident AF, multivariable models

Variables	HR (95% CI)	P
All subjects		
Estimated-GFR, 10 mL/min per 1.73 m^2 decline	1.02 (1.00-1.03)	.03
GFR categories		P for trend
≥60 mL/min per 1.73 m^2	1	0.007
30-59 mL/min per 1.73 m^2	1.29 (1.05-1.58)	
<30 mL/min per 1.73 m^2	1.42 (0.81-2.51)	
Subjects without treated hypertension or diabetes		
Estimated GFR, 10 mL/min per 1.73 m^2 decline	0.99 (0.97-1.01)	0.43
GFR categories		P for trend
≥60 mL/min per 1.73 m^2	1	0.04
30-59 mL/min per 1.73 m^2	1.26 (0.93-1.70)	
<30 mL/min per 1.73 m^2	1.96 (0.82-4.73)	

Models were adjusted for age, sex, body mass index, systolic and diastolic blood pressure, treated hypertension and diabetes.

Table IV. Baseline characteristics of study subjects, according to the AF at baseline

	No AF (n = 234 150)	AF (n = 1694)
Age, y	60.5 ± 12.1	69.9 ± 7.7
Female sex, n (%)	159,836 (68)	543 (32)
Body mass index, kg/m^2	22.8 ± 3.0	23.1 ± 3.0
Blood pressure, mm Hg		
Systolic	129.6 ± 17.9	131.8 ± 22.5
Diastolic	75.4 ± 11.0	78.7 ± 11.4
Serum creatinine, mg/dL		
Men	0.76 ± 0.13	0.81 ± 0.14
Women	0.58 ± 0.11	0.61 ± 0.11
Estimated GFR, mL/min per 1.73 m^2		
Men	101.4 ± 22.5	91.8 ± 20.2
Women	105.2 ± 25.5	95.8 ± 28.2
Antihypertensive drug, n (%)	44,905 (19)	565 (33)
Diabetes, n (%)	13,652 (6)	194 (11)

Plus-minus values are means ± SD.
$P < .001$ for all comparisons between groups.

covariates were associated with the development of AF (Table III). Subjects with GFR <60 mL/min per 1.73 m^2 were at a higher risk of new-onset AF compared to those without (HR 1.38; 95% CI, 1.14-1.66; $P < .001$). Among three groups according to the baseline GFR (≥60, 30-59, and <30 mL/min per 1.73 m^2), the risk of AF increased linearly as the GFR declined (Figure 2, Table III). Because hypertension and diabetes are risk factors for AF[17,19] we also studied the association of kidney disease with AF among 172 938 subjects without treated hypertension or diabetes. The risk of AF also increased linearly as the GFR declined in these subjects (Figure 2, Table III).

Table V. Incidence of kidney disease by AF

	No AF	AF
Development of kidney dysfunction		
All subjects	6.8 (6.6-6.9)	18.2 (15.2-21.2)
Subjects without treated hypertension or diabetes	5.2 (5.0-5.3)	16.6 (13.0-20.2)
Development of proteinuria		
All subjects	10.0 (9.8-10.1)	29.7 (25.8-33.6)
Subjects without treated hypertension or diabetes	7.7 (7.5-7.8)	24.8 (20.4-29.3)

Values are incidence per 1000 person-y (95% CI). AF indicates AF.

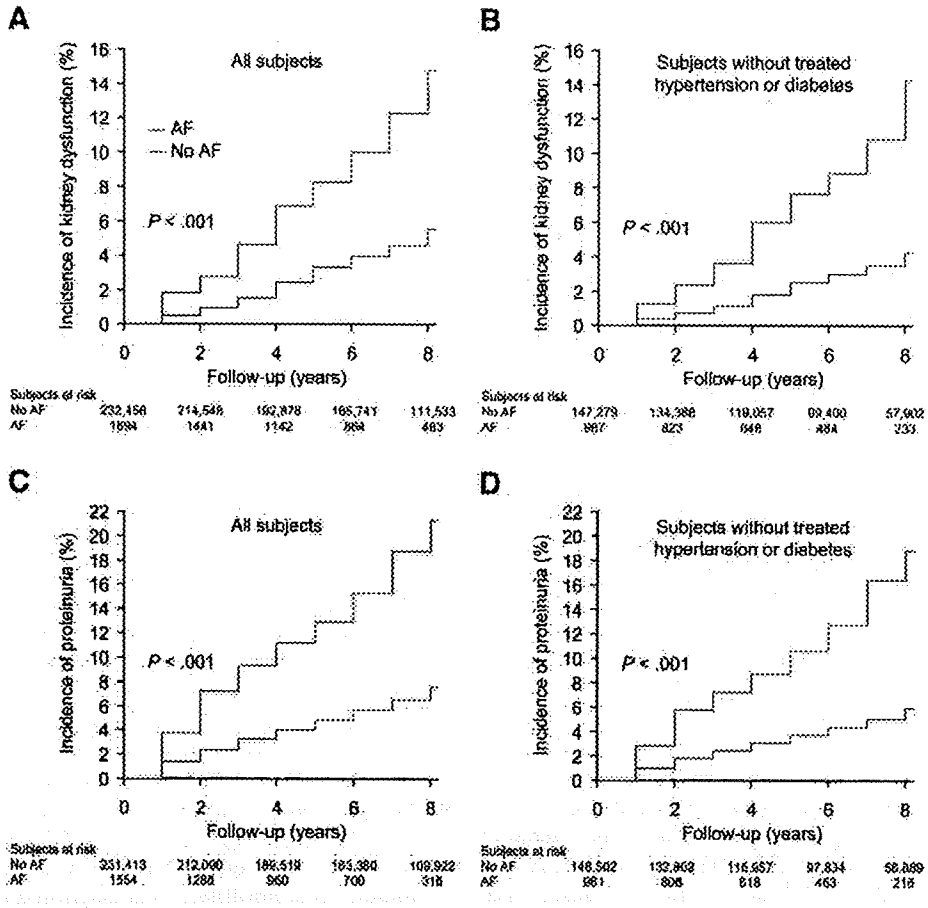
Association of AF with development of kidney disease

Among 234 150 subjects, there were 1694 subjects (0.7%) having baseline AF (Table IV). At baseline, subjects with AF had higher serum creatinine level and lower GFR than those without AF. The prevalence of treated hypertension or diabetes was higher in subjects with AF than those without AF.

During a mean follow-up of 5.9 ± 2.4 years, 7791 subjects (3.3%) developed kidney function decline. The incidence of kidney dysfunction was higher in subjects with AF than those without (Table V, Figure 3). In univariate models, increasing age, male sex, body mass index, systolic and diastolic blood pressure, treated hypertension, diabetes, and baseline AF were associated with new onset of kidney dysfunction. In multivariate models, baseline AF and all of other covariates except for diastolic blood pressure were associated with the development of kidney dysfunction (Table VI). Because hypertension and diabetes are strong risk factors for chronic kidney disease,[22,23] we also studied the association of AF with kidney disease among 148 246 subjects without treated hypertension or diabetes. In this cohort, the incidence of the development of kidney dysfunction was also higher in subjects with AF than those without (Table V, Figure 3) and AF was associated with the development of kidney dysfunction (Table VI).

During follow-up, 11 307 subjects (4.9%) developed proteinuria. The incidence of proteinuria was higher in subjects with AF than those without AF (Table V, Figure 3). In univariate models, increasing age, male sex, body mass index, systolic and diastolic blood pressure, treated hypertension, diabetes, and baseline AF were associated with new onset of proteinuria. In multivariate models, baseline AF and all of other covariates except for diastolic blood pressure were associated with the development of proteinuria (Table VI). Among 147 463 subjects without treated hypertension or diabetes, the incidence of the development of proteinuria was also higher in subjects with AF (24.8 per 1000 person-years) than those without (7.7 per 1000 person-years, Table V, Figure 3), and AF was associated with the development of proteinuria (Table VI).

Figure 3



Cumulative risk of developing kidney disease by baseline AF. Incidence of kidney dysfunction increased as baseline GFR decreased in all subjects (**A**) and in subjects without treated hypertension and diabetes (**B**). Incidence of proteinuria also increased as baseline GFR decreased in all subjects (**C**) and in subjects without treated hypertension and diabetes (**D**).

Table VI. Atrial Fibrillation and risk of chronic kidney disease and proteinuria, Multivariate Models

Variables	HR (95% CI)	*P* value
Development of kidney dysfunction		
All subjects	1.80 (1.54-2.10)	<.001
Subjects without treated hypertension or diabetes	2.22 (1.81-2.72)	<.001
Development of proteinuria		
All subjects	2.16 (1.92-2.42)	<.001
Subjects without treated hypertension or diabetes	2.42 (2.06-2.83)	<.001

Models were adjusted for age, sex, body mass index, systolic and diastolic blood pressure, treated hypertension and diabetes in all subjects and were adjusted for age, gender, body mass index, and systolic and diastolic blood pressure in subjects without treated hypertension or diabetes.

Discussion

In this general population of adults, we have shown a close association between AF and kidney disease: kidney disease was associated with the development of AF and AF was associated with the development of kidney disease. Although hypertension and diabetes are known as strong risk factors for subsequent AF and kidney disease,[17,18,20,21] both associations remained significant in subjects without hypertension or diabetes.

Associations have previously been described between AF and chronic kidney disease.[12-16] Atrial fibrillation is a common arrhythmia in end-stage kidney disease requiring hemodialysis and the duration of hemodialysis is a predictor of AF.[12-14] Similarly, serum creatinine level before cardiac surgery is a risk factor for the development