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ORIGINAL CONTRIBUTIONS

Additive Interaction of Metabolic Syndrome and Chronic Kidney Disease on Cardiac Hypertrophy, and Risk of Cardiovascular Disease in Hypertension

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BACKGROUND

Recent epidemiologic analyses have demonstrated a link between the metabolic syndrome (MetS) and chronic kidney disease (CKD). We examined the association between MetS, CKD, and left ventricular hypertrophy (LVH), and prospectively investigated the predictive value of the combination of MetS and CKD for cardiovascular disease (CVD) in essential hypertension.

METHODS

A total of 1,160 essential hypertensive patients (mean age 63 years, 53% male) underwent clinical evaluation, laboratory testing, and Doppler echocardiography, and were monitored for a mean follow-up of 4.8 years.

RESULTS

At baseline, total subjects were divided into four groups according to the presence/absence of MetS and/or CKD, and, compared to the group without MetS and CKD ($MetS^-/CKD^-$); those with MetS and CKD ($MetS^+/CKD^+$) had a multivariate-adjusted odds ratio of 2.40 (95% confidence interval (CI) 1.66–3.48) for LVH. During the follow-up period, 172 subjects developed CVD. Multiple Cox regression analysis including LV mass index (LVMI) showed that the presence of MetS as well as that of CKD were each independent predictors of CVD (hazard ratio 1.90 for MetS, 1.82 for CKD). We then divided the total subjects into four groups, and found that, compared to the $MetS^-/CKD^-$ group, multivariate-adjusted HR for the $MetS^+/CKD^+$ group was 3.58 (95% CI 2.14–5.95).

CONCLUSIONS

Our findings suggest that, in essential hypertension, the combination of MetS and CKD is a strong risk for LVH as well as a strong and independent predictor of subsequent CVD. These findings highlight the clinical importance of the concomitance of MetS and CKD in essential hypertension.

Keywords: blood pressure; cardiovascular disease; chronic kidney disease; hypertension; left ventricular hypertrophy; metabolic syndrome; risk factor

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Hypertension is a common risk factor for cardiovascular disease (CVD), and the cardiovascular prognosis in patients with hypertension depends not only on the level of blood pressure (BP), but also on the presence of associated risk factors. In the past few years, there has been growing attention to a condition known as the metabolic syndrome (MetS),[1] which is characterized by a cluster of atherosclerotic risk factors, including obesity, hypertension, insulin resistance, and dyslipidemia, as well as chronic kidney disease (CKD).[2] Individuals with MetS or CKD are at increased risk of CVD as well as death from CVD and all causes.[3–8] Furthermore, recent epidemiologic analyses have demonstrated a link between MetS and CKD.[9–11] However, whether the concomitance of MetS and CKD contributes to the development of CVD is unknown.

Echocardiography is a well-established procedure to diagnose increased left ventricular (LV) mass, and its presence is thought to increase CVD risk through a series of unfavorable metabolic, functional, and structural cardiac changes.[12–14] The assessment of LV geometry in addition to LV hypertrophy (LVH) is important for evaluation of the peculiar hemodynamic pattern such as a combination of pressure and volume stimuli, contractile efficiency, and prognosis.[15] Insulin resistance, oxidative stress, and inflammation have been implicated in the pathogenesis of MetS and CKD, which also have been shown to be associated with LVH. Increased LV mass has been shown to be associated with MetS and CKD;[16–20] however, we could not find any previous studies examining the hypothesis that the combination of MetS and CKD may be a strong risk for LVH.

The influence of increased LV mass on the association of MetS and/or CKD with CVD is also unknown. The

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association between MetS or CKD and increased CVD could be mediated through increased LV mass, and this may be one of the pathways linking MetS and CKD to CVD. Therefore, in this study, we investigated the potential interrelationship between MetS, CKD, and the risk of LVH in essential hypertensive subjects. Furthermore, we also examined prospectively whether MetS and CKD interact to substantially increase the risk of CVD in hypertension. Moreover, we additionally examined whether this association would be independent of LV mass.

METHODS

Study subjects. This study enrolled essential hypertensive patients in normal sinus rhythm, who had good-quality echocardiographic recordings, and monitored them for a mean follow-up of 4.8 ± 2.7 years. In our laboratory (the National Cardiovascular Center in Osaka, Japan), all hypertensive patients attended the echocardiography laboratory, and echocardiographic data were routinely collected consecutively. From 1,263 patients at the time of the baseline examination, we excluded patients with missing data of MetS or CKD components (n = 77) and patients receiving regular hemodialysis therapy (n = 26), leaving 1,160 patients (545 women) for this analysis. Exclusion criteria included acute coronary syndrome, congestive heart failure (CHF) (New York Heart Association class II or greater), secondary hypertension, moderate or severe aortic or mitral regurgitation, heart rate ≥100 bpm, and low ejection fraction (<45%). All procedures in this study were carried out in accordance with institutional and national ethical guidelines for human studies. All participants enrolled in this study were Japanese, and all gave informed consent to participate.

Baseline clinical characteristics. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg on repeated measurements, or receiving antihypertensive treatment. Diabetes mellitus was defined according to the American Diabetes Association criteria.[21] Smoking status was determined by interview, and defined as never-smoker, past-smoker (those with a history of habitual smoking but had quit), and current-smoker. Previous CVD was defined as a history of myocardial infarction, CHF, or stroke.

After fasting overnight, BP was measured with an appropriate arm cuff and a mercury column sphygmomanometer on the left arm after a resting period of at least 10 min in the supine position. After BP measurement, venous blood and urine sampling from all subjects was performed. Height and body weight were measured, and body mass index (BMI) was calculated. The following parameters were also determined: triglycerides, high-density lipoprotein cholesterol, C-reactive protein (CRP), and creatinine.

Definition of MetS and CKD. MetS was defined according to the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel with modification for body size.[1]

In this study, all patients were hypertensive and thus, participants had MetS if they fulfilled two or more of the following.

1. Elevated BMI (in lieu of waist measurement, which was not available in our database). The frequency of BMI ≥30 kg/m^2 is 2–3% in Japan and 20–30% in Western countries.[22–24] 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 in Western populations) according to the criteria of the Japan Society for the Study of Obesity.[22,25]
2. Elevated triglycerides (≥150 mg/dl).
3. Low high-density lipoprotein cholesterol (<40 mg/dl in men, <50 mg/dl in women).
4. Impaired fasting glucose (fasting plasma glucose ≥110 mg/dl and/or a history of diabetes).

The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease formula in ml/min. CKD and its stages were defined according to the guidelines of the National Kidney Foundation classification of CKD,[2] which defines from eGFR of <60 ml/min/1.73 m^2 or dipstick proteinuria (≥1+) as follows: eGFR ≥90 ml/min/1.73 m^2 without proteinuria (high BP), eGFR 60–89 ml/min/1.73 m^2 without proteinuria (high BP with reduced GFR), eGFR ≥90 ml/min/1.73 m^2 with proteinuria (stage 1), eGFR 60–89 ml/min/1.73 m^2 with proteinuria (stage 2), and stages 3–5 were classified according to the level of kidney function (eGFR 30–59, 15–29, and <15 ml/min/1.73 m^2, respectively), regardless of the presence of other markers of kidney damage.[2] Subjects were diagnosed with CKD if they were classified as CKD stage 1–5.

Echocardiographic methods and calculation of derived variables. Phased-array echocardiography with M-mode, two-dimensional, pulsed, and color-flow Doppler capabilities was performed in all study participants, as previously described.[26,27] Estimates of LV mass were calculated according to the American Society of Echocardiography criteria[28] applied to the formula of Devereux *et al.*[29] LV mass index (LVMI) was calculated by dividing LV mass by body surface area. LVH was defined as LVMI >125 g/m^2 for men and >110 g/m^2 for women.[30] Relative wall thickness (RWT) was calculated as (interventricular septal + posterior wall thickness)/LV internal diameter.[31] Concentric remodeling was defined as normal LVMI with RWT >0.45 (ref. 31). Eccentric hypertrophy was defined as LVH with RWT ≤0.45. Concentric hypertrophy was defined as LVH with RWT >0.45 (ref. 32). LV filling was assessed by recording mitral flow by a standard pulsed Doppler technique, and the following parameters were considered: the ratio of peak early-to-late diastolic filling velocity (E/A ratio) and the deceleration time of early diastolic LV filling.

Clinical end points. For survival analysis, observation began on the date of echocardiography, with verified dates updated through October 2007. All of the subjects were followed at

the National Cardiovascular Center in Osaka and treated by implementation of standard lifestyle and pharmacological measures. CVD events of interest in this study were acute myocardial infarction, stroke, aortic dissection, CHF requiring hospitalization, and cardiovascular death. The occurrence of myocardial infarction was confirmed if symptoms met the criteria of the World Health Organization and if the event was associated with abnormal levels of cardiac enzymes and diagnostic electrocardiographic criteria. Stroke was confirmed if the participant had a new neurologic deficit that persisted for >24 h. Computed tomographic scans or magnetic resonance images were available for all the events and were used to distinguish hemorrhagic from ischemic events. Aortic dissection was defined as any nontraumatic dissection when a participant was admitted to hospital with a dissection that required intervention, and diagnosis was based on confirmatory imaging, intraoperative visualization, or autopsy. CHF was defined by the Framingham Heart Study criteria,[33] which require the simultaneous presence of at least two major criteria, or one major criterion in conjunction with two minor criteria, and requiring treatment with a diuretic, vasodilator, or antihypertensive drug. The cause of death was classified as CVD if there was sudden death from CVD. All CVD events were determined by an independent review panel of physicians who were unaware of the echocardiographic and clinical findings. Events that were more equivocal, such as unrecognized myocardial infarction, were not included as CVD for this analysis. Furthermore, patients with clinical evidence of pneumonia or uremia were excluded. For patients who experienced multiple nonfatal episodes of CVD, the analysis included only the first event.

Statistical analysis. Statistical analyses were performed with SPSS, version 15.0 (SPSS, Chicago, IL). Data are presented as mean ± s.d. for continuous variables and as proportions for categorical variables. First, we divided the participants into four groups according to the presence/absence of MetS and/or CKD. Differences in baseline characteristics among the four groups were determined by one-way analysis of variance (ANOVA) with Dunnett's multiple comparison post-test for continuous variables, and χ^2 test for categorical variables. Because of the right skew in CRP distribution, levels of CRP were log-transformed to examine the significance of any difference between groups. The number of subjects in whom CRP was measured was small (n = 997) compared with the total number of study subjects. Therefore, CRP was not included in the following analysis.

We used logistic regression analysis to determine the odds ratio (OR) of LVH as a function of MetS or CKD. In multivariate models, we entered both MetS and CKD into the same model, and included variables that might confound the relation between LVH and MetS or CKD: age, sex, duration of hypertension, systolic BP, smoking status, previous CVD, and receiving antihypertensive medication. We next divided the subjects into four groups according to the presence/absence of MetS and/or CKD, and the relative ORs of LVH were assessed in crude, age- and sex-adjusted, and multivariate regression models (adjusting for the same variables as listed above). Relative ORs were calculated using the $MetS^-/CKD^-$ group as a reference for each.

Survival analysis was performed using cumulative event-free Kaplan–Meier curves according to the presence/absence of MetS or CKD, and the groups were compared by Mantel log-rank test. Cox proportional hazard analysis was used to examine the association between variables and the cumulative incidence of CVD in crude and multivariate models. In multivariate models, both MetS and CKD were entered into the same model after accounting for relevant variables, using a P value of <0.05 as the selection criterion. These effects were measured by the hazard ratio (HR) and 95% confidence interval (CI) based on Cox regression models.

We then evaluated the joint associations of MetS and CKD with incident CVD by dividing the subjects into four groups according to the presence/absence of MetS and/or CKD. Event-free survival analysis was performed using the Kaplan–Meier method to plot the cumulative incidence of CVD. The relative risk of CVD events in Cox proportional hazard analysis was assessed in crude and multivariate models, and the cumulative incidence of CVD was calculated using the $MetS^-/CKD^-$ group as a reference for each. In these analyses, HRs of CVD were calculated using the whole participants or excluding subjects with previous CVD and/or diabetes from the analysis. A P value <0.05 was considered to be statistically significant.

RESULTS

Characteristics of study subjects

The baseline clinical and biochemical characteristics of the study subjects are shown in **Table 1**. Their mean age was 63.3 ± 11.2 years, and 53.0% were men. Overall, 42.4% had MetS, and 50.6% had CKD. We first divided the subjects into four groups according to the presence/absence of MetS and/or CKD. As a result, the total subjects were divided into four groups as follows; no MetS and no CKD ($MetS^-/CKD^-$), MetS without CKD ($MetS^+/CKD^-$), CKD without MetS ($MetS^-/CKD^+$), and MetS and CKD ($MetS^+/CKD^+$). As shown in **Table 1**, compared with the $MetS^-/CKD^-$ group, the $MetS^+/CKD^+$ group showed an increased risk of cardiovascular morbidity, such as significantly longer duration of hypertension, higher prevalence of previous CVD, diabetes, and current-smoking, higher age, BMI, systolic BP, fasting glucose, and CRP, worse dyslipidemia, and lower eGFR. In addition, the $MetS^+/CKD^+$ group showed a significantly longer duration of hypertension, lower eGFR, and higher CRP than the $MetS^+/CKD^-$ group, and a significantly higher prevalence of diabetes, higher BMI, fasting glucose, and CRP, and worse dyslipidemia than the $MetS^-/CKD^+$ group.

Relations of MetS and CKD to LVH

The baseline echocardiographic characteristics of the study subjects are shown in **Table 2**. At baseline, 58.3% of the total subjects were found to have LVH. Univariate logistic

Table 1 | Baseline clinical characteristics of study subjects

Variables	Total	MetS$^-$/CKD$^-$	MetS$^+$/CKD$^-$	MetS$^-$/CKD$^+$	MetS$^+$/CKD$^+$
n	1,160	344	243	324	249
Age, years	63.3 ± 11.2	61.4 ± 11.4‡	60.4 ± 10.3‡	66.5 ± 10.9**,†	64.6 ± 10.7**,†
Male, %	53.0	46.5†	59.3**	50.3	59.4**
Duration of hypertension, years	16.2 ± 10.9	14.3 ± 10.3††	15.8 ± 10.8	16.4 ± 11.1*	18.8 ± 11.1**,†,††
Previous CVD, %	25.5	15.7‡	22.6††	31.8**,***	33.7**,***
Diabetes, %	25.0	6.4†	38.3**,‡	12.0†	54.6**,‡
Smoking status, % (never/past/current)	50.9/28.6/20.4	62.5†/21.2***/16.3†	39.9**,‡/31.3*/28.8**,‡	53.9†/28.8/17.3†	42.2/35.7**/22.1
BMI, kg/m^2	24.2 ± 3.4	23.4 ± 2.7†,‡	26.8 ± 3.2**,‡	22.3 ± 2.7**,†	25.4 ± 3.2**,‡
Systolic BP, mm Hg	145.2 ± 15.6	145.8 ± 14.6†	140.9 ± 13.4**,‡	148.0 ± 17.8†	147.8 ± 17.1†
Diastolic BP, mm Hg	81.6 ± 10.6	83.6 ± 10.9***,††	81.4 ± 9.4*	80.9 ± 10.7**	80.3 ± 10.9**
Pulse rate, bpm	66.6 ± 8.2	67.1 ± 8.5	66.2 ± 7.8	66.4 ± 8.4	66.4 ± 7.8
Triglycerides, mg/dl	138 ± 90	105 ± 48†	178 ± 124**,‡	105 ± 44†	187 ± 103**,‡
HDL-cholesterol, mg/dl	49.88 ± 15.08	57.62 ± 14.31†,††	42.15 ± 10.05**,‡	54.91 ± 15.08*,†	39.83 ± 11.60**,‡
Fasting glucose, mg/dl	102 ± 24	97 ± 15†	113 ± 30**,‡	94 ± 19†	108 ± 27**,***,‡
eGFR, ml/min/1.73 m^2	64.4 ± 31.3	82.0 ± 18.1***,‡	87.1 ± 22.8*,‡	44.3 ± 25.4**,†	44.0 ± 30.2**,†
CRP (mg/l), median (IQR), *n* = 997	0.70 (0.30–1.80)	0.50 (0.30–1.00)†,‡	1.00 (0.31–2.00)**	0.70 (0.28–1.70)**	1.20 (0.30–2.50)**,***,††
MetS components, %					
Obesity	36.1	19.2†	72.4**,‡	12.0†	55.4**,†,‡
Elevated triglycerides	31.9	9.0†	58.9**,‡	10.5†	65.1**,‡
Low HDL-cholesterol	40.1	12.2†	67.9**,‡	19.4†	78.3**,***,‡
Impaired fasting glucose	31.4	11.9†	50.2**,‡	15.1†	61.0**,†,‡
CKD stages					
High blood pressure	15.3	26.2‡	35.8‡	0**,†	0**,†
High blood pressure with reduced GFR	35.3	73.8‡	64.2‡	0**,†	0**,†
Stages 1 and 2	9.5	0‡	0‡	17.0**,†	22.1**,†
Stage 3	23.4	0‡	0‡	52.5**,†	40.6**,†,‡
Stages 4 and 5	16.6	0‡	0‡	30.5**,†	37.3**,†,††
Antihypertensive medication, %					
Calcium-channel blockers	68.2	54.1†,‡	68.3**	71.0**	83.9**,†,‡
β-Blockers	30.1	24.4	32.1	31.5	34.1*
ACE inhibitors or ARB	35.1	30.8	32.5	34.3	44.6**,***,††
Diuretics	18.1	10.2‡	10.3‡	25.3**,†	27.3**,†
No. of CVD events	172	21***,‡	33*	53**	65**,†,‡

Values are mean ± s.d. or frequency (%). IQR is 25th to 75th percentile.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-cholesterol, high-density lipoprotein cholesterol; MetS, metabolic syndrome.
$^{*}P < 0.05$ and $^{**}P < 0.01$ vs. MetS$^-$/CKD$^-$. $^{***}P < 0.05$ and $^{†}P < 0.01$ vs. MetS$^-$/CKD$^-$. $^{††}P < 0.05$ and $^{†}P < 0.01$ vs. MetS$^-$/CKD$^+$.

regression analysis found that the presence of MetS as well as CKD was each associated with an increased risk of LVH (MetS: OR 1.54, 95% CI 1.21–1.95; CKD: OR 1.83, 95% CI 1.44–2.31, $P < 0.01$, respectively). When MetS and CKD were entered into the same model, the results of multivariate logistic regression analysis showed that MetS as well as CKD was each an independent risk for LVH (MetS: adjusted-OR 1.58, 95% CI 1.22–2.05; CKD: adjusted-OR 1.52, 95% CI 1.18–1.96, $P < 0.01$, respectively).

We then divided the total subjects into four groups, and found that echocardiographic characteristics also differed between the groups, with the MetS$^+$/CKD$^+$ group

Table 2 | Echocardiographic characteristics of study subjects according to presence/absence of MetS and/or CKD

Variables	Total	MetS$^-$/CKD$^-$	MetS$^+$/CKD$^-$	MetS$^-$/CKD$^+$	MetS$^+$/CKD$^+$
% Fractional shortening, %	41.2 ± 6.9	41.8 ± 6.7	41.6 ± 7.0	40.8 ± 6.8	40.3 ± 7.2*
LV mass index, g/m^2					
Male	138.4 ± 38.1	122.1 ± 26.0***,‡	131.5 ± 29.4*,‡	148.4 ± 43.4**,†	150.2 ± 40.6**,†
Female	120.8 ± 33.2	111.8 ± 24.5***,††	121.0 ± 27.6*	120.0 ± 33.9*	137.8 ± 42.5**,†,‡
LV hypertrophy, %	58.3	46.2***,‡	57.5*	61.0**	71.5**,†,††
Relative wall thickness	0.48 ± 0.09	0.46 ± 0.08‡	0.48 ± 0.08	0.48 ± 0.09**	0.50 ± 0.09**
LV geometric patterns, %					
Normal geometry	21.4	30.2†,††	17.9**	21.0*	13.6**
Concentric remodeling	20.4	23.6	24.6	18.0	14.9*,***
Eccentric hypertrophy	17.9	15.7	19.2	19.5	18.5
Concentric hypertrophy	40.3	30.5††	38.3	41.5*	53.0**,†,††
E/A ratio	0.85 ± 0.25	0.91 ± 0.28‡	0.87 ± 0.24	0.84 ± 0.24**	0.80 ± 0.24**,†
DcT, ms	229.7 ± 51.8	221.7 ± 46.9	225.3 ± 47.8	230.3 ± 50.8	244.4 ± 62.0**,†,††

Values are mean ± s.d. or frequency (in %).
CKD, chronic kidney disease; DcT, deceleration time of early diastolic LV filling; *E/A*, ratio of peak early-to-late diastolic filling velocity; LV, left ventricular; MetS, metabolic syndrome.
*P < 0.05 and **P < 0.01 vs. MetS$^-$/CKD$^-$, ***P < 0.05 and †P < 0.01 vs. MetS$^-$/CKD$^-$, and ††P < 0.05 and †P < 0.01 vs. MetS$^-$/CKD$^+$.

Table 3 | Results of crude and multivariate logistic regression analysis relating MetS and CKD to LVH

	MetS$^-$/CKD$^-$	MetS$^+$/CKD$^-$	MetS$^-$/CKD$^+$	MetS$^+$/CKD$^+$
Crude	1 (reference)	1.55 (1.11–2.17)**	1.81 (1.33–2.47)**	2.91 (2.05–4.12)**
Age- and sex-adjusted	1 (reference)	1.59 (1.14–2.22)**	1.69 (1.24–2.32)**	2.80 (1.97–3.99)**
Multivariate-adjusted[a]	1 (reference)	1.58 (1.11–2.24)*	1.51 (1.09–2.10)*	2.40 (1.66–3.48)**

Values are odds ratio (95% CI).
CKD, chronic kidney disease; LVH, left ventricular hypertrophy; MetS, metabolic syndrome.
[a]Adjusted for age, sex, duration of hypertension, systolic BP, smoking status, previous CVD, and receiving antihypertensive medication.
*P < 0.05 and **P < 0.01 vs. MetS$^-$/CKD$^-$.

demonstrating significantly lower % fractional shortening and *E/A*, higher LVMI and RWT, lower prevalence of normal geometry, higher prevalence of concentric remodeling and concentric hypertrophy, and longer deceleration time of early diastolic LV filling than the MetS$^-$/CKD$^-$ group (Table 2). In addition, the MetS$^+$/CKD$^+$ group showed significantly longer deceleration time of early diastolic LV filling than the MetS$^+$/CKD$^-$ group as well as the MetS$^-$/CKD$^+$ group. The prevalence of LVH also significantly differed among groups, with the highest prevalence of LVH in the MetS$^+$/CKD$^+$ group. As shown in Table 3, concomitance of MetS and CKD was significantly associated with increased odds ratios of LVH. Multivariate analysis showed that the odds ratio of LVH was 2.4-fold higher in the MetS$^+$/CKD$^+$ group compared with the MetS$^-$/CKD$^-$ group.

Predictive value of MetS and CKD for CVD

During a mean (±s.d.) follow-up of 4.8 ± 2.7 years, 172 patients (14.8%, 70 female) developed CVD. Specifically, there were 38 patients with nonfatal CHF, 65 with cerebral infarction, 14 with intracerebral hemorrhage, 3 with subarachnoid hemorrhage, 18 with myocardial infarction, 6 with aortic dissection, and 28 patients died from CVD causes.

MetS and CKD were both associated with incident CVD events, with significance in log-rank tests of $P < 0.001$. A univariate Cox proportional hazard model showed that both MetS (HR 1.83, 95% CI 1.35–2.48, $P < 0.01$) and CKD (HR 2.71, 95% CI 1.96–3.74, $P < 0.01$) were each significant predictors of CVD events. Other variables in this study that significantly predicted CVD events included age, sex, duration of hypertension, previous CVD, smoking habit, systolic BP, LVMI (Table 4), antihypertensive medication (HR 1.81 for yes, 95% CI 1.07–3.07, $P < 0.01$), and LV geometry (concentric remodeling: HR 1.74, 95% CI 1.04–2.91, $P < 0.05$; eccentric hypertrophy: HR 1.22, 95% CI 0.69–2.14, NS; concentric hypertrophy: HR 2.19, 95% CI 1.39–3.43, $P < 0.01$). When MetS and CKD were entered into the same model, the results of multivariate Cox regression analysis including age, sex, duration of hypertension, previous CVD, smoking habit, systolic BP, LVMI, and antihypertensive medications found that the presence of MetS (HR 1.90, 95% CI 1.38–2.63, $P < 0.01$) as well as CKD (HR 1.82, 95% CI 1.29–2.59, $P < 0.01$) was each an independent predictor of CVD events. Furthermore, adjustment for LV geometry instead of LVMI did not meaningfully influence the results (MetS: HR 1.82, 95% CI 1.32–2.50; CKD: HR 2.02, 95% CI 1.43–2.84, $P < 0.01$, respectively).

Table 4 | Crude and multivariate-adjusted HRs of CVD events associated with MetS and CKD

	Total subjects						Subjects without previous CVD and/or diabetes ($n = 745$)					
	Crude		Multivariate adjusted[a]		Plus LVMI		Crude		Multivariate adjusted[b]		Plus LVMI	
Variables, unit of increase	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
MetS and CKD												
$MetS^-/CKD^-$	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
$MetS^+/CKD^-$	2.31 (1.34–4.00)	0.003	2.09 (1.19–3.66)	0.010	2.03 (1.16–3.57)	0.013	2.64 (1.30–5.35)	0.007	2.74 (1.34–5.62)	0.006	2.65 (1.29–5.44)	0.008
$MetS^-/CKD^+$	3.32 (2.00–5.50)	<0.001	2.21 (1.31–3.71)	0.003	2.08 (1.23–3.51)	0.006	3.22 (1.69–6.15)	<0.001	2.40 (1.23–4.62)	0.009	2.31 (1.19–4.46)	0.013
$MetS^+/CKD^+$	5.21 (3.19–8.53)	<0.001	3.85 (2.33–6.37)	<0.001	3.58 (2.16–5.95)	<0.001	5.25 (2.77–9.94)	<0.001	4.42 (2.32–8.42)	<0.001	4.16 (2.16–8.02)	<0.001
Age, 1 year	1.07 (1.05–1.09)	<0.001	1.06 (1.04–1.08)	<0.001	1.06 (1.04–1.08)	<0.001	1.08 (1.05–1.11)	<0.001	1.07 (1.05–1.10)	<0.001	1.07 (1.05–1.10)	<0.001
Sex, male	1.71 (1.26–2.33)	0.001	1.28 (0.84–1.95)	0.25	1.19 (0.78–1.81)	0.43	1.13 (0.74–1.72)	0.57				
Duration of hypertension, 1 year	1.02 (1.01–1.04)	0.001	1.01 (0.99–1.02)	0.45	1.00 (0.99–1.02)	0.56	1.02 (1.00–1.04)	0.08				
Previous CVD, yes	2.43 (1.79–3.29)	<0.001	1.69 (1.23–2.33)	0.010	1.67 (1.21–2.29)	0.002						
Smoking status												
Never	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Past	1.76 (1.25–2.49)	0.001	1.27 (0.82–1.96)	0.29	1.27 (0.82–1.95)	0.28	1.34 (0.81–2.21)	0.25	1.20 (0.73–1.99)	0.47	1.18 (0.71–1.95)	0.53
Current	1.81 (1.23–2.66)	0.002	1.69 (1.06–2.71)	0.029	1.58 (0.99–2.52)	0.06	1.69 (1.00–2.86)	0.049	1.63 (0.95–2.78)	0.08	1.53 (0.89–2.65)	0.13
Systolic BP, 10 mm Hg	1.14 (1.05–1.25)	0.003	1.10 (1.00–1.21)	0.041	1.07 (0.97–1.17)	0.18	1.16 (1.03–1.30)	0.018	1.12 (1.00–1.26)	0.05	1.10 (0.98–1.25)	0.12
Pulse rate, 10 bpm	1.13 (0.94–1.28)	0.17					1.16 (0.89–1.36)	0.23				
LVMI, 10 g/m^2	1.09 (1.05–1.12)	<0.001			1.05 (1.01–1.09)	0.024	1.08 (1.03–1.13)	0.001			1.06 (1.00–1.12)	0.045

Values are hazard ratio (95% CI).
[a]Adjusted for age, sex, duration of hypertension, previous CVD, smoking status, and systolic BP. [b]Adjusted for age, smoking status, and systolic BP.
BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; LVMI, left ventricular mass index; MetS, metabolic syndrome.

Joint effect of MetS and CKD on CVD

To explore the combined effects of MetS and CKD, we divided the total subjects into four groups on the basis of the presence or absence of MetS and/or the presence or absence of CKD at baseline. Life table analyses of CVD throughout the follow-up period in the four groups are plotted in **Figure 1**. These curves show significantly poorer survival in the $MetS^+/CKD^+$ group. **Table 4** shows the results from a series of crude and multivariate regression analysis, showing how the association of MetS and CKD with CVD risk changed as groups of CVD risk factors were added to the regression model. In the crude model, the risk for CVD was significantly higher in the $MetS^+/CKD^+$ group compared with the $MetS^-/CKD^-$ group (HR 5.21). The relative risk in the $MetS^+/CKD^+$ group remained highly significant in the multivariate model (HR 3.85). The further addition of LVMI to the model reduced the relative risk in the $MetS^+/CKD^+$ group to 3.58. Furthermore, when compared with the $MetS^+/CKD^-$ group or with the $MetS^-/CKD^+$ group, the risk of CVD events was significantly higher in the $MetS^+/CKD^+$ group in univariate Cox regression analysis (vs. $MetS^+/CKD^-$ group: HR 2.26, 95% CI 1.48–3.43, $P < 0.01$; vs. $MetS^-/CKD^+$ group: HR 1.57, 95% CI 1.09–2.26, $P = 0.01$) and in multivariate Cox regression analysis including LVMI (vs. $MetS^+/CKD^-$ group: HR 1.97, 95% CI 1.29–3.02; vs. $MetS^-/CKD^+$ group: HR 1.72, 95% CI 1.18–2.51, $P < 0.01$ respectively).

We performed several additional analyses to address the robustness of these findings. Because patients with previous CVD and/or diabetes were more frequent in the $MetS^+/CKD^+$ group, we repeated our analysis for the 745 patients without previous CVD and/or diabetes. In this analysis, 87 CVD events

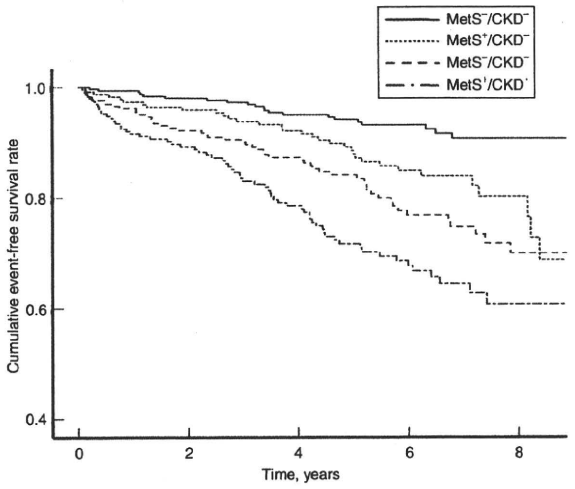

Figure 1 | Kaplan–Meier plots showing cumulative CVD event-free survival in subjects in four groups divided by presence or absence of MetS and presence or absence of CKD (log-rank $\chi^2 = 54.55$; $P < 0.001$). CKD, chronic kidney disease; CVD, cardiovascular disease; MetS, metabolic syndrome.

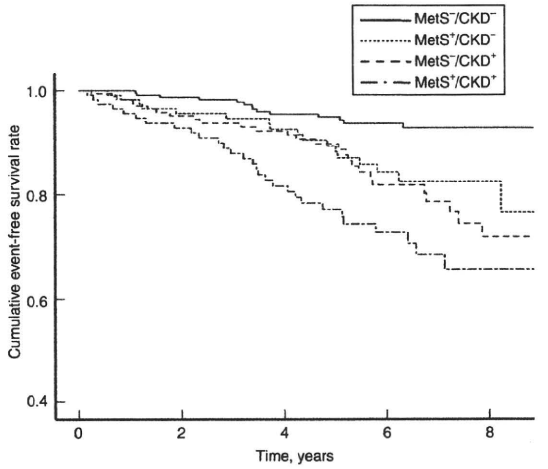

Figure 2 | Kaplan–Meier plots for CVD event-free survival in subgroup without previous CVD and or diabetes ($n = 745$) (log-rank $\chi^2 = 30.67$; $P < 0.001$). CKD, chronic kidney disease; CVD, cardiovascular disease; MetS, metabolic syndrome.

(11.7%, 47 female) occurred during the follow-up period. As shown in **Figure 2** and **Table 4**, the independent predictive value of MetS$^+$/CKD$^+$ for CVD events was also confirmed by the Kaplan–Meier method and by multivariate Cox regression analysis including LVMI. Furthermore, even when compared with the MetS$^+$/CKD$^-$ group or with the MetS$^-$/CKD$^+$ group, the risk of CVD events was significantly higher in the MetS$^+$/CKD$^+$ group in the multivariate model including LVMI (vs. MetS$^+$/CKD$^-$ group: HR 1.57, 95% CI 1.01–3.43, $P < 0.05$; vs. MetS$^-$/CKD$^+$ group: HR 1.81, 95% CI 1.06–3.08, $P = 0.03$).

DISCUSSION

This study identified a significant positive relationship between the combination of MetS and CKD and risk for LVH. This relationship was independent of age, sex, and other potential risk factors for LVH, such as smoking. We also examined the associations of the presence of MetS and CKD, alone and in combination, with incident CVD over a follow-up period, and found that the presence of MetS as well as CKD was each associated with CVD, with a joint effect that was greater than the individual effect of either disease separately. Despite previous studies suggesting a link between these two diseases,[9–11] these two risk factors interact to substantially increase the risk of CVD.

Our findings confirm previous investigations by documenting that the prevalence of LVH is higher in subjects with MetS or CKD than in those without these diseases.[16–20] Little information is available on the association of the combination of MetS and CKD with LVH, especially in essential hypertensives. In our study, LVH and altered LV patterns were more frequent in the MetS$^+$/CKD$^+$ group than in the MetS$^-$/CKD$^-$ group. Even after adjustment for confounding factors, MetS$^+$/CKD$^+$ was associated with a 2.4-fold higher risk of LVH than was MetS$^-$/CKD$^-$. The mechanism by which the concomitance of MetS and CKD is a strong risk for LVH remains hypothetical, but is likely multifactorial. Hypertension is the fundamental trigger of the sequence of biologic events that lead to the development of LVH. In addition, demographic characteristics (i.e., age and gender), volume overload, inotropy, obesity, and arterial compliance also are important determinants of the development and degree of LVH. In MetS, among the main nonhemodynamic factors that may contribute to the development of LVH, the most likely candidates are insulin resistance, activated sympathetic nervous system, increased arterial stiffness,[18,34] and inflammation.[35] In CKD, increased activity of the renin–angiotensin–aldosterone system and sympathetic nervous system, hypervolemia, hyperparathyroidism, abnormalities of calcium-phosphate homeostasis, and anemia may all contribute to the increase in LV mass.[36,37] Consequently, hemodynamic changes, such as increased peripheral resistance and hypervolemia, and nonhemodynamic factors including metabolic and hormonal factors have been proposed as possible factors contributing to LVH in subjects with MetS$^+$/CKD$^+$. Conversely, because the balance between the two fundamental hemodynamic stimuli (pressure and volume) also determines the predominant type of LV geometry, our result that a high prevalence of concentric hypertrophy was found in the MetS$^+$/CKD$^+$ group suggests the presence of increased total peripheral resistance[38] and activation of the renin–angiotensin–aldosterone system[39] in this group.

Our results were partially in accordance with the previous report that MetS is associated with subsequent CVD, independent of traditional CVD risk factors including LVH defined by electrocardiogram and serum creatinine.[40] We also found that, in essential hypertensives, the presence of MetS as well as CKD was each an independent predictor of CVD, and the combination of MetS and CKD was a strong and significant predictor of CVD. Moreover, the increased risk for CVD was evident even after excluding subjects with previous CVD and/or diabetes. Our results suggest that these diseases jointly contribute to the development of CVD, and the adverse prognostic effect of the combination of MetS and CKD was independent of traditional

CVD risk factors including LVMI. Hypertension is a potential cause and consequence of CVD, and thus, our results indicate the need for metabolic screening as well as the assessment of renal function in hypertensive patients. Several LVH-related factors may also ultimately contribute to the development of CVD, and a number of underlying biochemical derangements may exist in hypertensive patients with MetS and CKD.

One notable result of this study is that, in the case of concomitant MetS and CKD, the risk of CVD became higher than that in the presence of MetS or CKD alone. Apart from renal and metabolic profiles, there are other possible mechanisms by which the risk for CVD became higher with concomitant MetS and CKD. Inflammation and oxidative stress have been implicated in the pathogenesis of CVD. Even though preliminary data, our results showed a significantly higher CRP level in the $MetS^+/CKD^+$ group than in the $MetS^+/CKD^-$ group as well as in the $MetS^-/CKD^+$ group. In addition, more severe impairment of LV relaxation was observed in the $MetS^+/CKD^+$ group, and this impaired relaxation is known to be associated with increased risk of CVD.[27,41] Consequently, we propose that, in the case of concomitant MetS and CKD, further activation of inflammation and the renin–angiotensin system,[39] increased total peripheral resistance,[38] and impaired relaxation may be caused, and thus enhance the risk of CVD.

Our study has several limitations. First, we used eGFR rather than directly measured GFR to define CKD. Although serum creatinine has been widely used in clinical practice for evaluating renal function, misclassification of individuals with borderline CKD also may have resulted in biased estimates. Second, the study subjects were a hospital-based rather than population-based cohort. Third, only baseline measurements of risk factors such as eGFR, lipids, and drug use were available for the present analysis. The metabolic profile may deteriorate over time, and, as a result, drug use may increase substantially during the follow-up period. Fourth, because waist circumference was not available in this study, we used BMI to establish the diagnosis of obesity, with adjustment for the Japanese population, as a component of MetS. However, a recent meta-analysis reported no difference in outcomes irrespective of whether waist circumference or BMI was used in the criteria for MetS to predict CVD events.[42]

We found that the combination of MetS and CKD represents a strong risk for LVH in essential hypertension. In addition, both MetS and CKD predict CVD, with their combination further increasing the risk, independent of baseline confounding factors including LVMI. From a practical standpoint, physicians should be aware that hypertensive patients with concomitant MetS and CKD are at increased risk for the development of CVD. In hypertension, assessment of MetS as well as CKD has appeal for improving the risk stratification for CVD in daily practice. A large prospective population-based study will be important to confirm our preliminary observations, and future studies should investigate whether aggressive pharmacological and lifestyle interventions in hypertensive patients with concomitant MetS and CKD can reduce their substantial CVD risk.

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Chronic kidney disease as an independent risk factor for new-onset atrial fibrillation in hypertensive patients

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Objective **Chronic kidney disease (CKD) has recently been recognized to be a powerful predictor of cardiovascular morbidity and mortality. Atrial fibrillation (AF), which is a common arrhythmia in hypertensives, is associated with increased risks of cardiovascular events and death. However, the association between CKD and the onset of AF has not been fully elucidated. The present study assessed the hypothesis that CKD may influence the onset of AF in hypertensives.**

Methods **A total of 1118 hypertensive patients (mean age, 63 years) without previous paroxysmal AF, heart failure, myocardial infarction, or valvular disease were enrolled. CKD was defined as decreased glomerular filtration rate (<60 ml/min per 1.73 m^2) and/or the presence of proteinuria (≥1+).**

Results **During follow-up periods (mean, 4.5 years), 57 cases of new-onset AF were found (1.1% per year). Kaplan–Meier curves revealed that the cumulative AF event-free rate was decreased in the CKD group (log-rank test $P<0.001$). By univariate Cox regression analysis, age, smoking, left atrial dimension, left ventricular mass index, and the presence of CKD were significantly associated with the occurrence of AF. Among these possible predictors, CKD (hazard ratio 2.18, $P=0.009$) was an independent determinant for the onset of AF in multivariate analysis. Advanced stages of CKD (stages 4 and 5) were strongly related to the increased occurrence of AF.**

Conclusion **The present study demonstrated that the complication of CKD, especially progressed renal dysfunction, was a powerful predictor of new-onset AF in hypertensive patients, independently of left ventricular hypertrophy and left atrial dilatation.** ***J Hypertens*** **28:1738–1744 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: atrial fibrillation, hypertension, kidney, proteinuria, renal function

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IVST, interventricular septal thickness; LA, left atrial; LV, left ventricular; LVDd, left ventricular diameter at end-diastole; LVD, left ventricular diameter at end-systole; PWT, posterior wall thickness; RAS, renin–angiotensin system

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Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia in patients with hypertension, even in the absence of antecedent valvular heart disease or coronary artery disease. AF is a significant risk factor for ischemic stroke and heart failure events, and is also associated with increased risks of total and cardiovascular death, especially due to stroke [1]. Therefore, the occurrence of AF in hypertensive patients not only decreases their quality of life but also has a considerable influence on their prognosis and survival. Older age, blood pressure levels, especially ambulatory systolic blood pressure, increased left ventricular (LV) mass, and increased left atrial (LA) size have been known to be risk factors for the onset of AF in hypertensive patients [2–5]. In particular, a previous study showed that age and LV mass were independent determinants of AF incidence in initially untreated patients with essential hypertension [3].

Renal impairment is a powerful predictor of cardiovascular prognosis. Decreased estimated glomerular filtration rate (eGFR) is clearly associated with the increase in future cardiovascular events [6]. Proteinuria, even microalbuminuria, also increases the risk of cardiovascular events and death [7]. Thus, the involvement of renal impairment in the development of cardiovascular disease has recently been noticed. However, no study has shown the association between the onset of AF and renal impairment in hypertensive patients. To assess the hypothesis that chronic kidney disease (CKD) may affect the incidence of AF, the present study investigated the influence of renal impairment and CKD on the new onset of AF in hypertensives.

Methods

Study participants

From 1263 consecutive hypertensive patients who underwent echocardiography at the Division of Hypertension and Nephrology of our hospital between February 1997 and October 2003, 1118 patients (580 men and 538 women; mean age, 63 years) with normal sinus rhythm

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who had had no history of previous paroxysmal AF and in whom biochemical and urinary data were simultaneously obtained were enrolled in the present study. Patients with various cardiac disorders such congestive heart failure, myocardial infarction, myocardial disease, pericardial disease, valvular heart disease, LV asynergy, or LV systolic dysfunction (fractional shortening <0.25) were excluded from this study. Individuals after permanent pacemaker implantation or patients receiving dialysis were also excluded. Hypertension was defined as a systolic blood pressure of 140 mmHg or more and/or a diastolic blood pressure of 90 mmHg or more by repeated measurements or when medication was taken for treatment of hypertension. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria, such as a fasting plasma glucose of 7.0 mmol/l or more and/or a plasma glucose level at 2 h after a 75-g oral glucose load of 11.1 mmol/l or more, or when medication was taken for treatment of hyperglycemia.

All procedures of the present study were carried out in accordance with institutional and national ethical guidelines for human studies. All participants enrolled in this study were Japanese, and all gave informed consent to participate in this study.

Echocardiography

A comprehensive two-dimensional echocardiography was performed using a cardiac ultrasound unit (Sonos 5500; Philips Medical Systems, Andover, Massachusetts, USA) as previously described [8]. Echocardiographic parameters were measured by the consensus of two experienced investigators who were blinded to the clinical data of the patients. Measurements included interventricular septal thickness (IVST), posterior wall thickness (PWT), LV diameter at end-diastole (LVDd), LV diameter at end-systole (LVDs), and LA diameter. LV fractional shortening was calculated as (LVDd-LVDs)/LVDd. LV mass was estimated using the formula validated by Devereux and Reichek [9]: LV mass $(g) = 1.04 \times \{(IVST + PWT + LVDd)^3 - LVDd^3\} - 13.6$. LV mass was normalized for body surface area and expressed as the LV mass index.

Clinical parameters

At the time of the echocardiographic examination, blood pressure, heart rate, and body mass were determined. Blood pressure was measured by a physician in a hospital outpatient clinic with the patient in a sitting position after over 10 min of rest, using an appropriate-size arm cuff and mercury sphygmomanometer. The first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively, and measurements were taken to the nearest 2 mmHg.

Peripheral blood and urine samples were obtained in the morning after an overnight fast. The serum creatinine level was determined by the enzymatic method and eGFR was calculated by the formula of the Modification of Diet in Renal Disease Study with a modified equation for Japanese [10]: eGFR (ml/min per $1.73\,m^2$) = $194 \times age^{-0.287} \times serum\ creatinin^{-1.094} \times 0.739$ (if woman). Urinary protein excretion was assessed by the dipstick test from spot urine samples.

CKD was defined as decreased eGFR less than 60 ml/min per $1.73\,m^2$ and/or the presence of proteinuria (≥1+). The classification of CKD stages was performed according to the guidelines of the National Kidney Foundation classification of CKD [11] as follows; eGFR 90 ml/min per $1.73\,m^2$ or more with proteinuria (stage 1), eGFR 60–89 ml/min per $1.73\,m^2$ with proteinuria (stage 2), and stages 3, 4, and 5 were classified by the levels of eGFR (30–59, 15–29, and <15 ml/min per $1.73\,m^2$, respectively), regardless of the presence of proteinuria.

Follow-up

After the initial assessment, all patients visited our hospital periodically (every 1–2 months) for the treatment of hypertension and concurrent diseases. The pulse and heart beat were checked at every examination. Individuals with irregular pulse or cardiac rhythm and/or patients with complaint of palpitation or chest discomfort received 12-lead electrocardiogram and 24-h Holter recordings. In addition, all patients received standard 12-lead electrocardiogram at least once a year. AF was defined as absence of P waves before each QRS complex, irregular atrial electrical activity with fibrillatory waves varying in size, shape and timing, and completely irregular RR intervals. New-onset AF as the study endpoint was defined as the first presentation of AF during follow-up. Transient postoperative AF, occurring as an isolated episode within one month after surgery, was not counted as an outcome event. Because newly documented AF, not the duration or persistence of the arrhythmia, was the outcome event of interest, no distinction was made between paroxysmal and persistent AF. For patients without any AF event, the date of censor was that of the last contact with the patient.

Statistical analysis

Statistical analysis was performed using StatView Version 5 Software (Abacus Concepts Inc., Berkeley, California, USA). Values were expressed as mean ± SD. An unpaired Student's *t*-test was used for comparison between the two groups. AF event-free curves were derived by means of the Kaplan–Meier method and were compared by log-rank test. Possible predictors of new-onset AF were tested by univariate Cox proportional hazards regression analysis. Then, a multivariate analysis was applied to identify independent predictors and their predictive power. Independent predictors of AF incidence were also evaluated by using a stepwise regression analysis. A value of $P < 0.05$ was accepted as statistically significant.

Table 1 Clinical characteristics of total participants ($n = 1118$)

Variable	
Age (years)	63 ± 11
Sex (men) (%)	52
Body mass index (kg/m^2)	24.3 ± 3.4
Duration of hypertension (years)	16 ± 11
Diabetes mellitus (%)	24
Smokers (current or past) (%)	48
Systolic blood pressure (mmHg)	146 ± 16
Diastolic blood pressure (mmHg)	82 ± 11
Heart rate (bpm)	67 ± 8
eGFR (ml/min per 1.73 m^2)	68 ± 32
Urinary protein	
(−) to (±) (%)	74
(1+) to (2+) (%)	16
≥(3+) (%)	10
Antihypertensive treatment	
Ca channel blockers (%)	69
RAS inhibitors (%)	35
β-blockers (%)	29
Diuretics (%)	17
Others (%)	13
Statin use (%)	29

Values are mean ± SD or percentage. eGFR, estimated glomerular filtration rate; RAS, rennin–angiotensin system.

Results

Patient characteristics

The clinical characteristics of all patients are summarized in Table 1. The average duration of hypertension of the patients was 16 ± 11 years, and they had had history of antihypertensive treatment of 11 ± 9 years as average. At baseline, 83% of the study patients were receiving antihypertensive drugs, and 17% were treated with diet and/or exercise therapy only. Ca channel blockers, rennin–angiotensin system (RAS) inhibitors (i.e., angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors), β-blockers, diuretics, and other classes of agents were used alone or in various combinations in 69, 35, 29, 17, and 13% of the study patients, respectively.

The mean duration of follow-up was 4.5 years (range, 0.1–9.1 years), for a total of 5079 patient-years of observation. During follow-up, 57 cases of new-onset AF were found, indicating the incidence was 1.1% per year. Of these 57 AF cases, 39 (68%) were symptomatic and the other 18 (32%) were asymptomatic at the time of the first documented event.

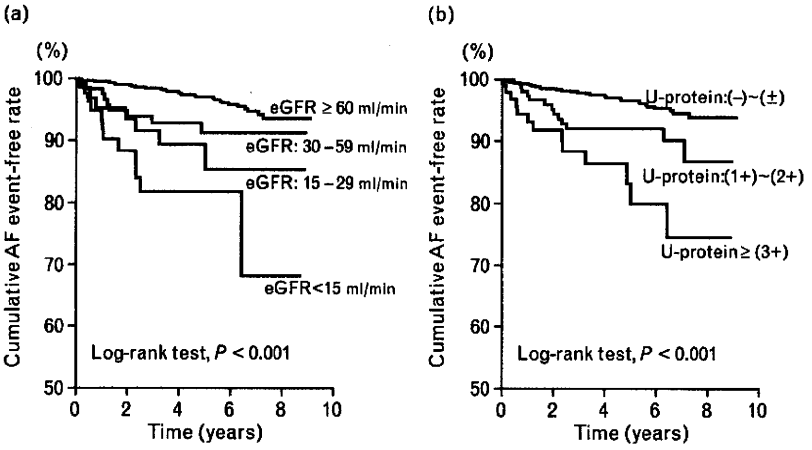
Relations of estimated glomerular filtration rate and proteinuria to the incidence of atrial fibrillation

The effect of eGFR and proteinuria on the incidence of new-onset AF was evaluated. The cumulative AF event-free rate was significantly decreased according to the reduction of basal eGFR (Fig. 1a). Likewise, AF event-free rate was clearly decreased according to the increase in urinary protein levels (Fig. 1b). In the Cox regression analysis, both eGFR (hazard ratio 0.82 per 10 ml/min per 1.73 m^2, $P < 0.001$) and proteinuria [(1+) to (2+): hazard ratio 2.31, $P = 0.012$; ≥(3+): hazard ratio 5.07, $P < 0.001$ vs. (−) to (±)] were significantly related to the incidence of AF.

Effect of chronic kidney disease on the incidence of atrial fibrillation

We divided the present patients into two groups by the absence or presence of CKD, which was defined as decreased eGFR less than 60 ml/min per 1.73 m^2 and/or the presence of proteinuria (≥1+). The participant group with CKD was associated with older age, higher

Fig. 1



Atrial fibrillation (AF) event-free curves obtained with the Kaplan–Meier method in the respective groups divided by basal estimated glomerular filtration rate (eGFR, a) or urinary protein levels (U-protein, b). (a) All participants were divided into four groups according to basal eGFR levels. Cumulative AF event-free rates in the groups with basal eGFR of ≥60 ($n = 818$), 30–59 ($n = 128$), 15–29 ($n = 73$), and <15 ml/min per 1.73 m^2 ($n = 99$) were 93.6, 91.2, 85.3, and 68.2%, respectively (log-rank test, $P < 0.001$). (b) All participants were divided into three groups according to basal U-protein levels. Cumulative AF event-free rates in the groups with basal levels of U-protein of (−) to (±) ($n = 827$), (1+) to (2+) ($n = 183$), and ≥ (3+) ($n = 108$) were 93.9, 86.7, and 74.7, respectively (log-rank test, $P < 0.001$).

Table 2 Comparison of basal characteristics between the two groups without and with CKD

	CKD (−) ($n=732$)	CKD (+) ($n=386$)
Age (years)	62 ± 11	65 ± 11*
Sex (men) (%)	47	61*
Body mass index (kg/m^2)	24.5 ± 3.4	23.8 ± 3.4*
Duration of hypertension (years)	15 ± 10	18 ± 11*
Diabetes mellitus (%)	18	35*
Smokers (current or past) (%)	44	55*
Systolic blood pressure (mmHg)	144 ± 15	150 ± 17*
Diastolic blood pressure (mmHg)	82 ± 11	81 ± 11*
Heart rate (beats/min)	67 ± 8	67 ± 8
eGFR (ml/min per 1.73 m^2)	83 ± 20	40 ± 30*
Urinary protein		
(−) to (±) (%)	100	25*
(1+) to (2+) (%)	0	47*
≥(3+) (%)	0	28*
Antihypertensive treatment		
Ca channel blockers (%)	61	83*
RAS inhibitors (%)	32	41*
β-Blockers (%)	26	35*
Diuretics (%)	10	30*
Statin use (%)	26	33*
LA diameter (mm)	36 ± 5	37 ± 5*
LV mass index (g/m^2)	121 ± 31	145 ± 44*
LV fractional shortening	0.42 ± 0.07	0.40 ± 0.07*

Values are mean ± SD or percentage. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; RAS, rennin–angiotensin system. *$P<0.05$ compared with CKD (−).

proportion of men, smaller body mass index, and higher rate of diabetes mellitus and smokers (Table 2). In addition, the patients with CKD had longer duration of hypertension, higher systolic blood pressure, and more use of antihypertensive drugs. As for echocardiographic parameters, LA diameter and LV mass index were significantly greater, and LV fractional shortening was slightly lower in patients with CKD than in those without CKD.

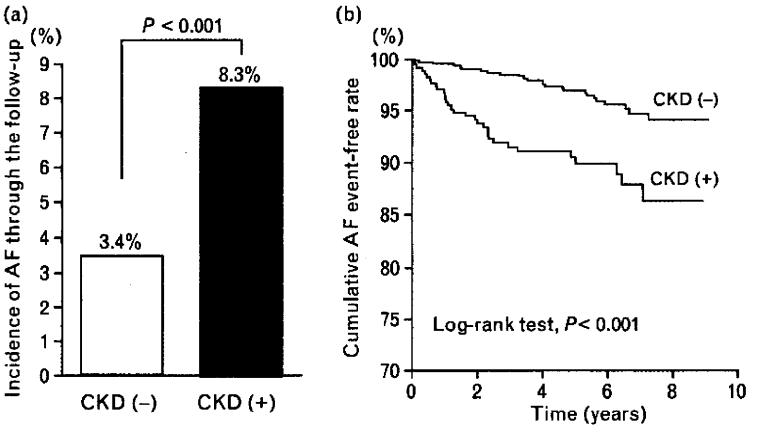
When comparing the incidence of new-onset AF between the two groups, the total incidence of AF through the follow-up periods was markedly higher in the patient group with CKD, compared to that without CKD (Fig. 2a). The cumulative AF event-free rate was also significantly decreased in the CKD group, compared to the non-CKD group (Fig. 2b).

As several confounding factors might be involved in the association between CKD and the incidence of AF in the present participants, we examined the independent predictors of new-onset AF by Cox regression analysis. In the univariate analysis, age, smoking, use of diuretic, LA diameter, LV mass index, and the presence of CKD were significantly related to the incidence of AF (Table 3). Among these possible predictive factors, age, smoking, and the presence of CKD were independent predictors of new-onset AF by the multivariate analysis. The adjusted hazard ratio of having CKD for new-onset AF during follow-up was 2.18 (95% confidence interval 1.21–3.90, $P=0.009$). Independent predictors of AF incidence were re-examined by stepwise regression analysis including all clinical and echocardiographic variables as possible independent factors. The presence of CKD as well as age, smoking, and LA diameter was an independent predictor of new-onset AF (age, hazard ratio 1.48 per 10 years, $P=0.008$; smoking, hazard ratio 1.92, $P=0.037$; LA diameter, hazard ratio 1.43 per 5 mm, $P=0.015$; CKD, hazard ratio 2.36, $P=0.004$).

Chronic kidney disease stages and the incidence of atrial fibrillation

The association of CKD stages with the incidence of AF was finally examined. In the univariate Cox analysis, the occurrence of new-onset AF was significantly increased in

Fig. 2



(a) Incidence of atrial fibrillation (AF) through the follow-up periods in the two groups without and with chronic kidney disease (CKD). The total rates of new-onset AF in the patients without and with CKD were 3.4% (0.7% per year) and 8.3% (2.1% per year), respectively ($P<0.001$). (b) AF event-free Kaplan–Meier curves in the two groups without and with CKD. Cumulative AF event-free rates in the non-CKD group and CKD group were 94.1 and 86.3%, respectively (log–rank test, $P<0.001$).

Table 3 Predictors of new-onset AF by univariate and multivariate Cox regression analysis

	Hazard ratio (95% CI)	P
Univariate analysis		
Age, 10 years	1.65 (1.24–2.19)	<0.001
Sex, men	1.51 (0.89–2.55)	0.128
Body mass index, 1 kg/m^2	1.01 (0.93–1.09)	0.839
Duration of hypertension, 1 year	1.02 (1.00–1.05)	0.100
Diabetes mellitus, yes	1.34 (0.75–2.40)	0.318
Smoking (current or past), yes	2.23 (1.29–3.84)	0.004
Systolic blood pressure, 10 mmHg	1.06 (0.90–1.25)	0.480
Diastolic blood pressure, 10 mmHg	0.88 (0.69–1.13)	0.316
Heart rate, 1 bpm	0.98 (0.94–1.01)	0.165
Ca channel blocker, yes	1.56 (0.84–2.89)	0.162
RAS inhibitor, yes	0.82 (0.47–1.44)	0.492
β-Blocker, yes	1.38 (0.81–2.35)	0.236
Diuretic, yes	2.23 (1.23–4.03)	0.008
Statin, yes	1.00 (0.57–1.76)	0.990
LA diameter, 5 mm	1.43 (1.10–1.87)	0.008
LV mass index, 10 g/m^2	1.09 (1.03–1.15)	0.004
LV fractional shortening, 0.01	0.98 (0.94–1.02)	0.250
CKD, yes	2.99 (1.77–5.05)	<0.001
Multivariate analysis		
Age, 10 years	1.54 (1.16–2.04)	0.003
Smoking (current or past), yes	1.78 (1.01–3.15)	0.047
Diuretic, yes	1.23 (0.65–2.32)	0.533
LA diameter, 5 mm	1.26 (0.94–1.68)	0.118
LV mass index, 10 g/m^2	1.03 (0.96–1.10)	0.457
CKD, yes	2.18 (1.21–3.90)	0.009

In the multivariate analysis, all variables that had a significant association in the univariate analysis were included as possible independent factors. AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; LA, left atrial; LV, left ventricular; RAS, rennin–angiotensin system.

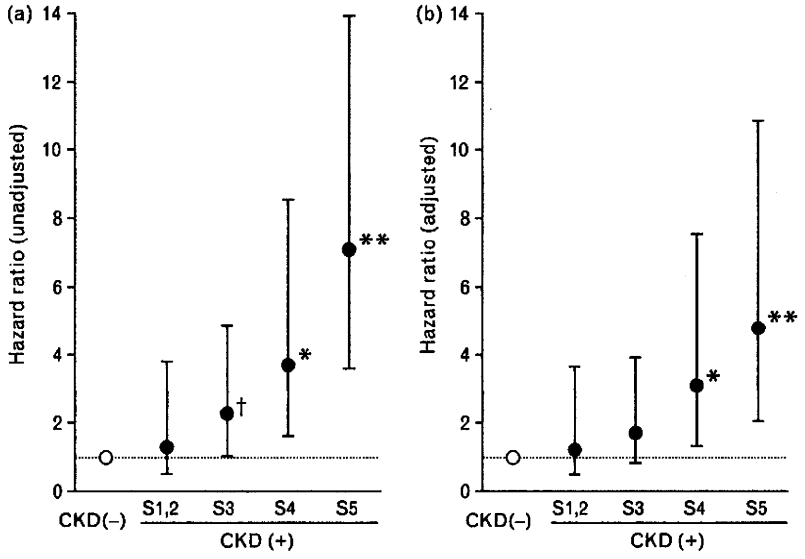
the participant groups with CKD stage 3 and more advanced stages (Fig. 3a). After adjustment for confounding factors (i.e., age, smoking, use of diuretic, LA diameter, and LV mass index) by the multivariate analysis, CKD stages 4 and 5 were still significantly associated with the increased incidence of AF (Fig. 3b).

Discussion

The present study has shown that CKD defined as decreased eGFR and/or the presence of proteinuria is longitudinally associated with the incidence of new-onset AF in hypertensive patients. Our results indicate that antecedent existing CKD has a significant influence on new-onset AF in hypertensives.

Several clinical and population-based studies showed that the prevalence of AF was independently associated with decreased eGFR and increased levels of urinary albumin [12–14], although these cross-sectional investigations did not elucidate whether antecedent renal dysfunction affects the incidence of AF. Prospective observational studies examining postoperative AF showed that renal impairment (decreased eGFR or renal failure) was associated with an increased risk of AF after cardiac surgery [15,16]. A recent study reported that decreased baseline eGFR was associated with an increased risk of subsequent new onset AF in a large scale of community-based cohort [17]. The findings of our study are fundamentally consistent with these observations. However, previous

Fig. 3



Relation of chronic kidney disease (CKD) stages to the incidence of atrial fibrillation (AF) evaluated by univariate (a) and multivariate (b) Cox regression analysis. Respective data present hazard ratios (open or solid circles) and the 95% confidence intervals (vertical lines) in the groups without CKD ($n = 732$) and with CKD stages 1–2 (S1,2, $n = 86$), 3 (S3, $n = 128$), 4 (S4, $n = 73$), and 5 (S5, $n = 99$). In the multivariate analysis, all variables that had a significant association in the univariate analysis (i.e., age, smoking, use of diuretic, left atrial diameter, and left ventricular mass index) were included as confounding factors. $^{\dagger}P < 0.05$, $^{*}P < 0.01$, $^{**}P < 0.001$ vs. CKD (–).

studies have shown that many factors are involved in the development of AF in a general population and patients with cardiovascular disorders [18–20]. As for hypertensive patients, it has been revealed that age, systolic blood pressure, LV mass, and LA size are related to the incidence of AF [2–5,21]. Thus, there was the possibility that these factors might mediate the association between CKD and AF incidence observed in the present and other studies, because GFR generally decreases with age, and pressure and volume load augmented by renal dysfunction directly increases LV mass and LA size. In fact, the present patients with CKD had older age, higher systolic blood pressure, and greater LV mass index and LA diameter, compared with those without CKD. In addition, age, LV mass index, and LA diameter as well as CKD were relating factors to the incidence of AF in the univariate Cox regression analysis of this study. By the multivariate analysis, however, the association of CKD with new-onset AF was warranted to be still significant independently of these confounders, although the adjusted hazard ratio of CKD for AF incidence was diminished compared to the crude risk ratio before adjustment. Therefore, the present study has demonstrated for the first time that the existence of CKD in hypertensive patients is an independent predictor of new-onset AF, apart from the effects of aging, LV hypertrophy, and LA dilatation.

Verdecchia *et al.* [3] showed that age and LV mass were the sole independent predictors of new-onset AF in a large cohort of initially untreated patients with essential hypertension. In our patients with chronically treated hypertension, LV mass index was not an independent determinant of the incidence of AF. The exact reason for the discrepant findings is unclear, but there was a possibility that antihypertensive treatment before the enrollment might have modified LV mass in our study.

In the univariate analysis of our study, basal systolic or diastolic blood pressure was not significantly related to the incidence of AF. Previous studies showed that systolic blood pressure and pulse pressure were good predictors of incident AF in large cohorts of the general population [22,23]. In hypertensive patients, however, there have been discrepant findings concerning the significant influence of blood pressure levels on the incident of AF [2–4,21]. Antihypertensive treatment and changes in blood pressure during follow-up might have modified the outcome and have spoiled the possible relation between systolic blood pressure and incident AF in our retrospective observational study. Since the present patients with CKD had a significantly higher systolic blood pressure than those without CKD, there might be a possibility that elevated blood pressure in the CKD group promoted renal dysfunction further, resulting in contribution of new-onset AF partly.

In the present study, the incidence of new-onset AF was clearly associated with the decrease in eGFR. In fact, CKD stages 4 and 5 were a significant predictor of incident AF after adjustment for confounding factors by the multivariate analysis. The incidence of AF was also increased according to the severity of proteinuria. Therefore, our findings suggested that advanced renal dysfunction including massive proteinuria chiefly contributed to the incidence of new-onset AF in the present hypertensive patients.

The causal mechanism by which renal impairment has a great and partly cardiac overload-independent influence on the occurrence of AF in hypertensive patients could not be drawn from our observational study, but there are some possible speculations. The increased risk of developing AF in CKD may be related in part to activation of signaling pathways of inflammation, because previous studies have shown that renal insufficiency is associated with elevations of inflammatory markers such as C-reactive protein [24] and that C-reactive protein predicts increased risk for developing future AF [25]. Possible involvement of oxidative stress and endothelial dysfunction in the development of AF has also been shown [26,27]. Since the patients with chronic renal failure have increased levels of oxidative stress markers and impaired endothelial function [28], oxidative stress and endothelial dysfunction caused by renal impairment may be involved in the increased risk of new-onset AF in patients with CKD. In addition, these mechanisms might be also involved in the association between smoking habit and incident AF observed in the present study, because smoking is known to increase oxidative stress and deteriorate endothelial function.

Limitations

Screening 24-h electrocardiographic recordings were not performed in our study, although standard 12-lead electrocardiograms were periodically done for all the present patients. Therefore, it is possible that asymptomatic cases of AF may have gone undetected. In fact, 68% of 57 cases of newly documented AF were accompanied by some symptom such as palpitation and chest discomfort, and the other 32% were asymptomatic cases in the present study. However, all patients visited our hospital periodically (every 1–2 months) and the pulse and heart beat were checked at every examination. Individuals with irregular pulse or cardiac rhythm received 12-lead electrocardiogram and 24-h Holter recordings, even they had no cardiac symptom. In addition, the incidence of new-onset AF in our study (1.1% per year) was similar to the incidence rates in other studies for patients with essential hypertension (0.5–1.7% per year) [3–5,21] and higher than those in middle-aged and elderly adults from population-based studies (0.2–1.1% per year) [17,18,22,23,29,30]. Thus, it is less likely that there were a considerable number of missed AF cases in the present study. Furthermore, since any misclassification or underdetection of incident AF is

expected to occur at random and independent of renal function, such misclassification would not overestimate the true risk of new-onset AF associated with CKD. The small number of new-onset AF during follow-up, however, must be considered as a limitation of the study, especially in comparing AF incidence rates among more than three groups.

Several studies have revealed that RAS inhibitor treatment and hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) use are associated with reduced incidence of AF in patients with cardiovascular disease [21,31,32]. As another study limitation, therefore, we must consider the possibility that these treatments might bias the outcome of the present study.

Moreover, there was a possibility that the obtained findings in this study might be limited to the Japanese population. Further studies are needed to validate our results in Western and other racial populations.

In conclusion, the present study demonstrated that CKD defined as decreased eGFR and/or the presence of proteinuria was associated with an increased risk of new-onset AF in hypertensive patients, and that the impact of CKD on the incidence of AF was independent of LV hypertrophy and LA dilatation. In particular, advanced stages of CKD were strongly related to the increasing occurrence of AF. In managing hypertensive patients, therefore, it may be important to prevent the progression of renal dysfunction in prevention of the occurrence of new-onset AF.

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There are no conflicts of interest.

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Opinion

Proposed Guidelines for Hypertriglyceridemia in Japan with Non-HDL Cholesterol as the Second Target

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The Japan Atherosclerosis Society (JAS) guidelines for the prevention of atherosclerotic diseases, proposing management for LDL cholesterol as the primary target, have successfully contributed to the prevention of cardiovascular events; however, recently, the impact of hypertriglyceridemia as an additional cardiovascular risk has become understood, especially in light of the rise in obesity, metabolic syndrome, and diabetes in the Japanese population. Rather than waiting to obtain conclusive domestic data confirming that hypertriglyceridemia is a cardiovascular risk factor and that its management is efficacious, we propose guidelines for hypertriglyceridemia using non-HDL cholesterol as a second target.

J Atheroscler Thromb, 2008; 15:116-121.

Key words; Hyperlipidemia, Dyslipidemia, Triglycerides, HDL cholesterol, LDL cholesterol

Introduction

Many prospective epidemiological studies have indicated a positive relationship between serum triglyceride (TG) levels and the incidence of coronary heart disease (CHD)[1, 2]. TG-rich lipoproteins such as remnant lipoproteins and small dense LDL particles are increased in hypertriglyceridemia and have been established to be atherogenic by numerous clinical and experimental studies[3-6]; however, classification of the plasma TG level as an independent risk factor for atherosclerosis has been controversial. This is partly because plasma TG levels are inversely intercorrelated by other well-established risk factors, such as low HDL cholesterol. To date, large scale trials for intervention targeting plasma TGs with TG reducing agents such as fibrates have not reached definitive conclusions about their effectiveness on primary endpoints, although fibrates have some impact on both primary and secondary prevention in small scale studies[7-9].

The precise estimation of plasma TGs as a cardiovascular risk is confounded by other risk factors, such as obesity, diabetes, hypertension and smoking. In addition, a cluster of metabolic risk factors, such as visceral obesity and insulin resistance with hypertriglyceridemia, referred to as metabolic syndrome, indicates that plasma TG concentrations are tightly linked to other strong risk factors for CHD. Thus, patients with elevated TGs are at increased risk for CHD, although greater risk cannot be independently explained by TGs. Meanwhile, recent meta-analyses suggested that plasma TGs could be an independent factor for CHD[1, 2]. Supportively, many experimental studies indicated that triglyceride-rich lipoproteins as well as LDL are atherogenic. Taken together, these data suggest that hypertriglyceridemia should be regarded as a semi-independent risk factor and should be included as a clinical target for the prevention of CHD. Considering the increasing prevalence of obesity, metabolic syndrome, and diabetes in this country, guidelines specialized for patients with hypertriglyceridemia need to be immediately established. In this study, we propose new guidelines for Japanese patients with hypertriglyceridemia

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Table 1. Plasma lipid profile of severe and mild type IIb hyperlipidemic patients sub-grouped by non-HDL cholesterol level

Male	severe type IIb non-HDLc >190 mg/dL	mild type IIb non-HDLc <190 mg/dL	p
n	51	54	
Total Cholesterol	270±41.8	234±40.3	0.001
Triglycerides	347±286	236±110	0.031
HDL Cholesterol	42.4±8.0	54.9±15.2	0.000
LDL Cholesterol	159±51.6	135±38.1	0.029
non-HDL Cholesterol	228±41.6	182±39.1	0.000
Female	**severe type IIb non-HDLc >180 mg/dL**	**mild type IIb non-HDLc <180 mg/dL**	**p**
n	52	48	
Total Cholesterol	265±29.6	231±20.2	0.000
Triglycerides	242±120	218±56	0.1
HDL Cholesterol	47.3±14.1	63.2±19.5	0.000
LDL Cholesterol	175±40.4	125±17.9	0.000
non-HDL Cholesterol	224±30.2	168±14.9	0.000

Subjects were patients who visited the outpatient clinic of the Endocrinology and Metabolism Unit of Tsukuba University Hospital on a regular basis (monthly or bimonthly) as described in Materials and Methods. Data are the means±SD (mg/dL).

using non-HDL as a secondary target after the goal for LDL cholesterol as the primary target is achieved.

Materials and Methods

A total of 1,124 patients in Tsukuba University hospital in 2006 were consecutively included in the study (Table 1). Patients with severe illness were excluded. Plasma total cholesterol (TC), LDL-C, TG, HDL-C, glucose and HbA1c in either the fasted or fed state were determined enzymatically with the Hitachi 7070. Plasma HDL-C concentration was measured by a direct method using polyethylene-glycoso-pretreated enzymes. We calculated LDL-C concentration with Friedewald's formula (TC-TG/5-HDL-C) when TG was less than 400 mg/dL. Plasma non-HDL-C concentration was calculated as TC−HDL-C. One hundred and five male and 100 female patients were diagnosed with Type IIb hyperlipidemia (TC>220 mg/dL and TG>150 mg/dL). They were subcategorized into two groups according to their non-HDL cholesterol level (Table 1).

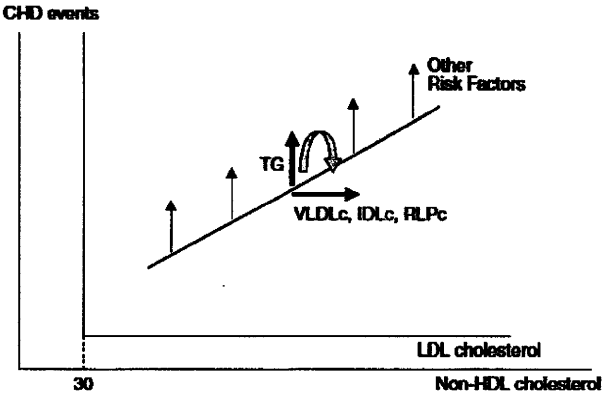

Fig. 1. Rationale for usage of non-HDL cholesterol: impact of TG and other risk factors on correlation between LDL-cholesterol CHD event.

nonHDL cholesterol=Total cholesterol−HDL cholesterol=VLDL cholesterol+IDL cholesterol (remnant lipoprotein cholesterol)+LDL cholesterol (Friedewald formula).
VLDL cholesterol+IDL cholesterol (RLP cholesterol)=TG/5
The risk of hypertriglyceridemia is approximated to VLDL, IDL, and RLP cholesterol estimated as TG/5, and incorporated into non-HDLC. The difference between non-HDL cholesterol and LDL cholesterol on X-axis was set up at 30 mg/dL based upon the data from Fig. 2.

Results and Discussion

Advantage of Non-HDL Cholesterol as a Marker for Hypertriglyceridemia

LDL cholesterol has been established as the most potent predictor of CHD and is currently the primary target for treatment and prevention. Other risk factors, including TG, diabetes, obesity, and metabolic syndrome, do not directly elevate plasma LDL cholesterol, but could enhance the risk of LDL cholesterol by shifting up the curve, as depicted in Fig. 1. To evaluate and manage the risk of hypertriglyceridemia, the TG level must be interpolated into the risk of plasma cholesterol. In patients with high TGs, most VLDL cholesterol resides in the smaller (remnant) VLDL fraction. Cholesterol of remnant lipoproteins (VLDL and IDL), which is concomitantly increased by elevation of plasma TG is an appropriate surrogate marker of hypertriglyceridemia. TG-rich remnant lipoproteins have been established as atherogenic lipoproteins[4, 5]. Thus, RLPc, a commercially available laboratory test for remnant lipoprotein cholesterol, could be a suitable marker for the atherogenicity of hypertriglyceridemia; however, this test is expensive and is not practical for use as a routine parameter. In contrast, non-HDL cholesterol, defined as total cholesterol−HDL cholesterol, is easily calculated, and represents the sum-

mation of VLDL/IDL (remnant) cholesterol and LDL cholesterol. It reflects the risks for all apoB-containing lipoproteins and could be an excellent marker for atherogenic lipoproteins. Plasma TG itself is not an appropriate marker for CHD risk due to its internal and dietary variability. In contrast, non-HDL cholesterol is not affected by dietary states and has much less daily variability than TG.

Predictive Power of Non-HDL Cholesterol

Non-HDL cholesterol reflects the risks of both hypertrigyceridemia and LDL-cholesterol[10, 11]. Several studies have indicated that non-HDL cholesterol is better than LDL cholesterol in its predictive power of cardiovascular diseases, indicating that VLDL cholesterol could contribute to CVD[12]. Non-HDL cholesterol is also a useful marker in a variety of subpopulations: men, the elderly, and patients with high-risk diseases such as diabetes and end-stage renal disease[13-16]. Our current clinical data from patients with type IIb hyperlipidemia also support the usefulness of non-HDL cholesterol (**Table 1**). In our outpatient clinic, 70% of patients had diabetes and roughly 10% were type IIb hyperlipidemia (cholesterol > 220 mg/dL and TG > 150 mg/dL). These type IIb hyperlipidemic patients were equally divided into two sub-groups: severe (non-HDL cholesterol levels ≥ 190 mg/dL for male patients and 180 mg/dL for female patients) and mild < 190 mg/dL for male patients and 180 mg/dL for female patients. When the severe and mild IIb groups were compared, total, LDL, HDL cholesterol, and TG levels were significantly different among these two groups for both genders, except for serum triglyceride in females (**Table 1**). These data indicate that non-HDL cholesterol is an excellent marker representing all the components of dyslipidemia. The usefulness of non-HDL cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy has been already recognized in the USA[17, 18]. Another candidate marker for both remnant and LDL cholesterol is plasma apoB level[19]. ApoB is a direct marker for the particle number of apoB-containing lipoproteins and reflects risks of both remnants and LDL. Non-HDL cholesterol is highly correlated with apoB, and should replace this specialized and expensive laboratory test despite some reports indicating that apoB is better than non-HDL cholesterol for the predictive power of CHD[13, 20].

However, according to the Friedewald formula, the TG risk in non-HDL cholesterol represents only one fifth of TG levels as remnant cholesterol, and thus, the contribution of the risk is relatively weak compared to that of LDL cholesterol. Our previous data indicated that the correlation of non-HDL cholesterol to LDL cholesterol was much stronger than that to the TG level (**Fig. 2**)[21]. It should be noted that non-HDL cholesterol is not a specific marker for hypertriglyceridemia. Rather, non-HDL cholesterol should be regarded as a general single marker for both hypercholesterolemia and/or hypertriglyceridemia.

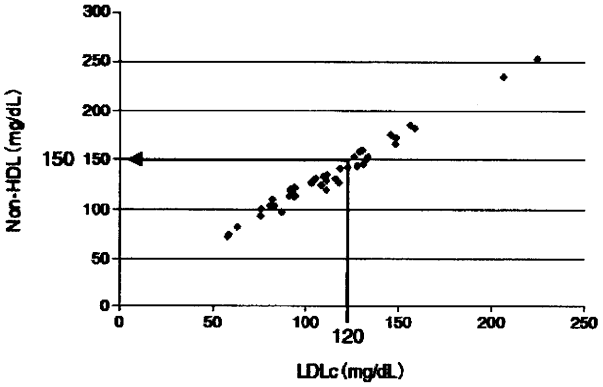

Fig. 2. Distribution of non-HDL cholesterol vs. calculated LDL cholesterol in normolipidemic patients.

Non-HDL cholesterol and LDL cholesterol calculated from Friedewald formula were highly correlated. Subjects were from the outpatient clinic of Tsukuba University Hospital[21].

Proposed Guidelines for Hypertriglyceridemia

Based upon these considerations, we propose guidelines for hypertriglyceridemia in Japanese patients using non-HDL cholesterol as a secondary target, as shown in **Table 2**. This is an extended version of the 2007 edition of the Japan Atherosclerosis Society (JAS) guidelines for the prevention of atherosclerotic diseases in which LDL cholesterol is the primary marker and target. It is essentially similar to the AHA-ATPIII guidelines for hyperTG in USA[22]. ATPIII recommends using non-HDL cholesterol as a secondary target when plasma TG is greater than 200 mg/dL because VLDL cholesterol is not significantly accumulated if TG is less than 200 mg/dL[23]. We do not have enough clinical data for Japanese on the relationship between TG and VLDL cholesterol to provide the appropriate TG level where the use of a non-HDL marker should be considered. Currently, we recommend using non-HDL for patients with hypertriglyceridemia (TG > than 150 mg/dL). Even for patients with hypertriglyceridemia, the primary target is still LDL cholesterol. In the 2007 JAS guidelines, goals of LDL for the secondary prevention group and the primary prevention group with category I, II, and III are 100, 120, 140, and 160 mg/

Table 2. Proposed Japanese Guidelines for Hypertriglyceridemia

Treatment	Categories		Goal for plasma lipids (mg/dL)		
		Coronary Risk Factors other than LCL-C	Primary LDL-C	Secondary nonHDL-C	HDL-C
Primary Prevention Improving lifestyle as the first line, followed by medication	I (Low Risk Group)	0	<160	<190	≥40
	II (Intermediate)	1~2	<140	<170	
	III (High)	≥3	<120	<150	
Secondary Prevention Improving lifestyle & medication	Past History of CHD		<100	<130	

Goals for control depend upon categories of LDL cholesterol and non-HDL cholesterol. The primary target in hypertriglyceridemia is LDL-cholesterol. If the goal for LDL-cholesterol in the Japanese Guidelines for Atherosclerosis 2007 is already achieved, nonHDL-C is the secondary target. For the patients with TG > 500 mg/dL, potential genetic disorders and the prevention of acute pancreatitis should be considered. Coronary risk factors other than LDL-cholesterol include low HDL cholesterol, aging, diabetes, hypertenstion, smoking, past history of CHD, and obesity (visceral obesity).

dL, respectively. Goals for non-HDL cholesterol in each group are those for LDL cholesterol plus 30 mg/dL. This is based upon our outpatient clinic data that non-HDL cholesterol was 30 mg/dL higher than LDL cholesterol (Fig. 2)[21]. ATPIII also recommends using LDL cholesterol goal + 30 mg/dL[24]. This also corresponds to the calculated VLDL cholesterol of the cut-off point of normal TGs (150/5 mg/dL). This goal is arbitrarily set and could be modified in the future, especially when the relative atherogenicity of remnants and LDL cholesterol are more precisely determined. In the case of TGs of greater than 500 mg/dL, the risk of pancreatitis should be carefully considered as a potential acute complication.

Treatment of Hypertriglyceridemia Based upon Non-HDL Cholesterol Level

Treatment of patients with hypertriglyceridemia for primary prevention should be initiated with lifestyle modifications, especially reducing weight and increasing physical activity. Lifestyles exacerbating hypertrigylyceridemia, such as overweight, obesity, physical inactivity, cigarette smoking, excess alcohol intake, and very high carbohydrate diets, need to be improved. Other disorders and drugs that cause secondary hypertriglyceridemia, including diabetes, chronic renal filure, nephrotic syndrome, and steroid therapy, should also be treated first. In the event that lifestyle modification for at least three months is not effective to achieve the goal of non-HDL cholesterol, medication should be considered. Currently, due to lack of evidence to fully justify the use of fibrates for high TGs prior to statins, it is recommended to use a statin as the first line choice for high non-HDL cholesterol. If statin therapy is already used to control LDL cholesterol, management of non-HDL should be targeted by increasing the dose of the statin or switching to a stronger form. This is based upon the notion that remnant lipoproteins, as well as LDL, are taken up through LDL receptors that are up-regulated by statins. In the case of type III hyperlipidemia, or if high non-HDL cholesterol is much more prominent than LDL cholesterol because of hypertriglyceridemia, fibrates could be considered as they specifically reduce plasma TGs and are effective against type III hyperlipidemia. However, LDL cholesterol should be carefully monitored since fibrates occasionally raise LDL cholesterol following a decrease in TGs (VLDL cholesterol). In case the goal for LDL cholesterol is not attainable, the addition of cholestimide and/or ezetimibe to statin could be considered, whereas EPA could be considered for hypertriglyceridemia. A positive result from a recent large scale Japanese study using both EPA and pravastatin to estimate the prevention of atherosclerotic events, justifies superimposing EPA on statin therapy, although the contribution of the plasma TG-lowering effect of EPA to the prevention of cardiovascular events is not yet determined[25]. The complexity of the choice of medication for high non-HDL cholesterol is currently inevitable because no agents specifically decrease non-HDL cholesterol. Drug information strongly warns against the use of both statins and fibrates because of increasing the risk of the life-threatening side effect of rhabdomyolysis. Joint use is justified only when the benefit exceeds the risk, which requires expertise in this field; however, considering the very few reports of rhabdomyolysis as a severe side effect in recent post-market studies in Japan, carefully prescribing both agents for high-risk patients such as those with type IIb hyperlipidemia could be re-considered. Joint use might be restricted in the elderly or renal compromised patients. In addition, monitoring mus-