Estimated Glomerular Filtration Ratio (eGFR) is better index than creatinine clearance (Cockcroft-Gault) for predicting prevalence of atrial fibrillation in general Japanese population

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ABSTRACT

Direct oral anti-coagulant (DOAC) has been used in patients with non-valvular AF, and renal function is recommended to be evaluated using the CCr (Cockcroft-Gault) as reduction criteria of DOAC. In contrast, estimated glomerular filtration rate (eGFR) is usually used as an index of renal function in the daily practice. We determined age- and gender-specific prevalence rate of AF, and whether CCr or eGFR was associated with the prevalence of AF. Data of 108,951 subjects were collected from the periodic health examination. Risk factors of AF were evaluated by the medical history, physical examination and blood sampling, and AF was diagnosed by the electrocardiography.

The prevalence rate of AF was 0.92% (998/108,951) and there was four times higher in men than in women and increased with age. Cardiac disease (odds ratio: OR = 27.07, confidential interval: CI 23.39-31.37, p = 0.0001), female (OR = 3.65, CI 3.11-4.30), age > 65 years old (OR = 2.52, CI 2.14-2.96), hyperlipidemia (OR = 2.51, CI 1.97-3.20), BMI >25 kg/m2 (OR=1.37, CI

1.19-1.58), hypertension (OR = 1.14, CI 1.11-1.16) were independently high risks of prevalence of AF in the multivariate logistic regression analysis, respectively. The odds ratio of the risk of having AF was significantly higher in eGFR≦59 (OR=2.10, CI: 1.21-3.86) than in eGFR≧90 but not CCr after adjustment of age, gender, diabetes mellitus and smoking. However, this significance disappeared after additional adjustment of hypertension. Cardiac disease, gender, aging, hyperlipidemia, obesity, hypertension and renal dysfunction were strong risk factors for prevalence of AF. The evaluation of renal dysfunction as a morbidity risk of atrial fibrillation was suggested that eGFR should be used.

Key words: atrial fibrillation, estimated glomerular filtration ratio, creatinine clearance, hypertension,

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia especially in old generation.[1] AF was frequently observed as comorbid disease in patients with hypertension, which was induced by several risk factors such as aging, left ventricular hypertrophy and left atrial enlargement.[2] Alternatively, aging, hypertension and diabetes mellitus were also associated with chronic kidney disease (CKD), which had the onset risk of AF[3] and would influence large impact of its prognosis.[4,5]

Recently, direct oral anti-coagulants (DOAC) have been used in the practical medicine, and the impaired renal function may lead to expression of bleeding complications in patients with administration of DOAC.[6,7] The index of renal function was creatinine clearance (CCR); the Cockcroft-Gault equation was specified in United State Food and Drug administration approved prescribing information of DOAC.[8] Although studies were limited to evaluate the relationship between CCr and adverse clinical outcomes in AF patients with anticoagulant,[9–11] the recent sub-analysis of Fushimi AF

registry demonstrated that the group of CCr<30 ml/min had significant higher stroke, systemic embolization and major bleeding rates than other groups (30<CCr<50 ml/min, 50 ml/min<CC) in the entire cohort and the cohort without oral anticoagulant.[12] In contrast, the early detection of kidney disease, a simple index; the estimated GFR (eGFR), which is calculated from creatinine and age have been used, and the lower levels of eGFR stages independently associated with the risks of death, cardiovascular events, and hospitalization.[13] However, to our knowledge, there was no study comparing CCr and eGFR for the onset risk of AF. Moreover, there was few current data that examined the prevalence of AF and the risk factor of AF in the large cohort. Therefore, we determined the age and gender-specific prevalence rate of AF, and revealed the risk factor of AF, and also compared which was better index of eGFR and CCr as evaluating renal function associated with the onset risk of AF.

METHODS

Subjects had periodic health examination of community resident and employees of companies and governments from April 2013 to March 2014 in Tochigi Prefecture, in Japan. The informed consents were written in all subjects. The study design was approval in the ethics community of the Tochigi Public Health Service Association, and data were collected from the database of this institution. The ethic committee of Dokkyo Medical University according to the Declaration of Helsinki also approved study protocol.

Symptom and medical history including hypertension, diabetes mellitus, dyslipidemia, cardiac disease and smoking habit were collected by the questionnaire. Each item was classified in 4 categories as follow: the currently treatment, only follow-up, completion of treatment and without treatment. The medical history was positive if there was more than one item. The smoking habit was defined as positive history of smoking within the past 5 years.

Physical examination including blood pressure, electrocardiography, blood

sampling (serum creatinine, fasting glucose, hemoglobin A1c, LDL-cholesterol, HDL-cholesterol, triglyceride, uric acid and hemoglobin), body weight and height was underwent. Blood pressure was measured in the sitting and resting position after few minutes. Body mass index was calculated as weight by square of height. Hypertension was defined as currently treatment of antihypertensive drugs and/or systolic blood pressure ≧140 mmHg or diastolic blood pressure ≧ 90 mmHg on healthy check-up. Diabetes mellitus was defined as currently treatment of oral hypoglycemic drugs and/or insulin, glucagon-like peptide-1 agonist or fasting blood glucose ≧126 mg/dl or/and HbA1c≧6.5%. Dyslipidemia was defined as currently treatment of hypolipidemic drugs or serum LDL-cholesterol ≧140 mg/dl and/or HDL-cholesterol<40 mg/dl and/or triglyceride≧150 mg/dl.

eGFR was calculated by the 3-variable Japanese equation: eGFR ($ml/min/1.73m^2$) = $194 \times Age^{-0.287} \times Serum\ creatinine^{-1.094} \times 0.739$ (if female).[14] Renal function were categorized by the eGFR level as ≧90, 60-89, ≦59.[15] CCr was also calculated by Cockcroft-Gault equation: CCr (ml/min) =

((140-Age) × Body weight)/(72 × Serum creatinine) × 0.85 (if female).[16] Another renal function was categorized by the CCr level as ≧80, 50-79, <50).[17-19]

AF was diagnosed by the automatic computerized analysis that was performed with the ECG recorder FCP-7431 (Fukuda Denshi, Tokyo, Japan) at the time of health examination. Conventional diagnostic criteria AF, i.e., a glossary irregular ventricular rhythm of supraventricular origin, no visible P wave and irregular fluctuation of the baseline, were employed. Almost of all subjects with AF who diagnosed by automatic ECG system were followed by hospital to confirm its diagnosis.

Statistical analysis

All continuous calculated data are expressed as the mean ± SD. Categorical data was presented proportion (%). Baseline characteristics differences between groups were analyzed by Student t test or analysis variance of continuous (ANOVA). The variables of AF risk were analyzed by

multivariate logistic regression analysis. Chi-square test was used for analyzing categorical variables with percentage (%). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated in all of the regression analyses. Multivariate regression analysis was used to evaluate the association between eGFR, CCr and prevalence of AF. First, all associations were adjusted by age and gender, additionally by hypertension, diabetes mellitus, cardiac disease and smoking. The relationships between eGFR or CCr and age or body mass index (BMI) were assessed by Pearson's correlation coefficient (r). Statistical analysis was performed using JMP 10.0 software (SAS Institute, Carry, NC, USA). Statistical significance was accepted at $p < 0.05$.

RESULTS

Total 108,951 subjects were registered in this cross sectional study. The number of including men and women were 54,645 and 54,306 respectively, which were almost equal. The total prevalence rate of AF was 0.92%

(998/108,951) and there was four times higher in men than in women (1.46% vs. 0.37%, p<0.0001). The prevalence of AF in for each decade of advancing age of men and women were shown in Table 1. Although the prevalence of AF increased with aging, that were higher in men than in women in each age group. Of note, AF was rare <60 years old in men (95/32,407: 0.29%) or <70 years old in women (62/44,609: 0.14%), respectively.

Baseline clinical characteristics in subjects with or without AF were shown in Supplementary table 1. Almost one-third of men and the half of women had palpitation or feeling irregular pulse in AF subjects. Hypertension, diabetes mellitus, dyslipidemia and cardiac disease were more frequently comorbid in subjects with AF than in those without AF in both genders, respectively (p<0.0001, respectively). Smokers were however, lesser in AF than non-AF subjects in men (p<0.0001) and women (p<0.05). Cardiac disease (odds ratio: OR = 27.07, confidential interval: CI 23.39-31.37, p = 0.0001), female (OR = 3.65, CI 3.11-4.30), age > 65 years old (OR = 2.52, CI 2.14-2.96, p = 0.0001), hyperlipidemia (OR = 2.51, CI 1.97-3.20, p = 0.0001),

BMI >25 kg/m2 (OR=1.37, CI 1.19-1.58, p = 0.0004), hypertension (OR = 1.14, CI 1.11-1.16, p = 0.001) were independently high risks of prevalence of AF in the multivariate logistic regression analysis, respectively as shown in Table 2. Furthermore, the logistic regression analysis of the continuous variables revealed that systolic blood pressure (odds ratio: OR=1.07, CI 1.03-1.11, p<0.0001) at the time of health examination was only positively associated with prevalence of AF.

There was baseline clinical characteristics when the CKD were categorized by the eGFR level as ≧90, 60-89, <59 were shown in Table 3. Total 85,414 subjects whose serum creatinine were available could be analyzed, and subjects with AF were 884 (1.04%). According to decreasing eGFR, the prevalence of atrial fibrillation as well as hypertension, dyslipidemia, cardiac disease, and systolic blood pressure increased, and it became elderly, body weights were however, almost similar as shown in Table 3.

If the odds ratio (OR) of the risk of having AF at the eGFR≧90 was calculated as 1, there was significantly high risks at eGFR 60-89 (OR=1.53,

CI: 1.14-2.12) and eGFR≦59 (OR=2.61, CI: 1.95-3.75) after adjustment of the age and gender. After additional adjustment of diabetes mellitus and smoking, there was still significantly high risk at eGFR≦59 (OR=2.10, CI: 1.21-3.86) as shown in Table 4. However, this significance disappeared after additional adjustment of hypertension. Thus, the hypertension was one of the strong covariates of risk of having AF in subject with eGFR≦59.

In contrast, there was baseline clinical characteristics when the renal function were categorized by the CCr level as ≧80, 50-79, <50 were shown in Table 5. Total 84,931 subjects could be analyzed, and subjects with AF were 861 (1.01%). According to decreasing CCr, the prevalence of atrial fibrillation as well as hypertension, dyslipidemia, cardiac disease, and systolic blood pressure increased, and it became elderly. Of note, body weights were decreased with lowering CCr as shown in Table 5.

If the odds ratio (OR) of the risk of having AF at the CCr≧80 was calculated as 1, the odd ratios did not differ among three groups after adjustment of the age and gender (CCr 50-79: OR=0.97, CI: 0.82-1.15, CCr<50: OR=0.91, CI:

0.70-1.17) as shown in Table 6. After additional adjustment of diabetes mellitus and smoking, there was significantly low risk at CCr<50 (OR=0.54, CI: 0.30-0.95). However, these significances disappeared after additional adjustment of hypertension (OR=0.70, CI: 0.42-1.14). Indeed, eGFR was inversely correlated with BMI ($r = -0.072$, $p<0.0001$), and CCr was positively correlated with BMI ($r = 0.458$, $p<0.0001$) when the relationship between eGFR, CCr and BMI was analyzed in all subjects, respectively (Supplementary figure 1). Therefore, the discrepancy between the results of eGFR and CCr might be caused by the difference of the body weight in terms of BMI in each classified group as shown in Table 3 and 5.

Finally, the associations between eGFR or CCr and age were shown in Figure1. Although both indexes gradually decreased with aging, CCr was higher than eGFR at younger than 70 years old. In contrast, CCr was lower than eGFR at older than 70 years old and then inverse association was observed on the border of the 70 years old.

DISCUSSION

This study evaluated the prevalence and risk factors of AF by using database of annually health checkup in the general population living in the middle part of Japan. The multivariate logistic regression analysis showed that female (OR = 3.65 vs. male), age > 65 years old (OR = 2.52 vs. < 65 years old) were independently high risks of prevalence of AF in this study. The prevalence of AF was 0.92% among aged ≥20 years. AF was rare <60 years old in men (0.29%) or <70 years old in women (0.14%), and there was four times higher in men than in women in this all population (1.46% vs. 0.37%). Thus, AF was strongly associated with age and gender.

The prevalence of AF for each decade of advancing age of men and women found in the present study are comparable with those previously reported.[16] However, our findings that the higher prevalence rate of AF was observed in the men from 60 to 80 years old and the women above 80 years old compared with those of previous report,[20] which might be relate that there was a difference of one decade between our study and those previous studies. In

our country, the prevalence of AF has been estimated to rise by the increase of the aging population.[20]

BMI >25 was also risk factor of the prevalence of AF (OR=1.37) in this study. Obesity has been associated to increased risk of AF, it was associated with a 4–5% increased risk of AF over a mean follow-up of 14 years, independently of hypertension, diabetes mellitus, and myocardial infarction in the Framingham Heart study.[21] This relationship may be mediated by an increase in left atrial diameter, which can be attenuated by weight loss.[22] Atrial stretch enhances the vulnerability of the atrium that trigger to AF.[23] The Women's Health study reported a linear relationship between BMI and AF, with a 5% increase in risk of AF for a 1-unit increase in BMI.[24]

Although our data showed that cardiac disease was complicated more frequently in both men and women with AF than in those without, the cardiac disease was simply collected by the questionnaire when there was more than one item: the currently treatment, only follow-up, completion of treatment and without treatment. Thus, the loan AF might be included in

the category of cardiac disease. For this reason, the rate of comorbidity with cardiac disease may be high in both genders in AF compared with previous studies. With the exception of cardiac disease, the complications of hypertension and diabetes mellitus were more than two times frequent in both men and women with AF compared with those without AF. Moreover, the multivariate logistic regression analysis demonstrated hypertension (OR = 1.14 vs. normotension) was independently high risk of prevalence of AF. It has also reported that hypertension is the most prevalent risk factor for incidence of AF[25-27] and was complicated more frequently with AF.[20] Of note, the stepwise regression analysis of the continuous variables revealed that SBP at the time of health examination (OR=1.07) was the independently associated with high risk of prevalence of AF in this study. Cardio-Sis trial demonstrated that new-onset atrial fibrillation occurred less in the blood pressure tight-control (SBP<130 mm Hg) than in the usual-control group (SBP<140 mm Hg) for two years treatment in hypertensive patients without diabetes mellitus.[28] Taken together, these data suggested that inadequate

antihypertensive treatment was unable to prevent AF.

Diabetes mellitus and other risk-factors were also comparable with those previously reported.[20] Diabetes mellitus (OR = 2.38, p <0.0001) was a significant risk factor of AF by the simple logistic regression analysis but not multivariate logistic regression analysis. It might be suggested that other confounding variables were stronger association with prevalence of AF.

In generally, it has been reported that reverse epidemiology, i.e. the cholesterol paradox, does exist between lipid profile and AF, whereby low level of HDL cholesterol and LDL-cholesterol or triglyceride are positively related to increasing AF.[29,30] The mechanism of this relationship was speculated by Suzuki.[31] Although the hyperlipidemia was collected by simply questionnaire, there was no association between lipid profile such as HDL, LDL cholesterols and triglyceride levels at the time of health examination and the prevalence of AF in this study (data was not shown).

Although the glomerular filtration rate (GFR) was estimated by creatinine clearance in the practical medicine, both indexes were strictly different.

Cockcroft-Gault formula (CCr) by using age, body weight, serum creatinine and gender was proposed.[16] Even in current, United States Food and Drug Administration recommends that drug dosage is adjusted by CCr in patients with impaired renal function, and do not approve to substitute estimated GFR (eGFR) in place of CCr for renal dosing of drugs.[8] Previously, serum creatinine was measured by the Jaffe method, which was higher than that by the current enzymatic assay, which makes to be slightly overestimation especially in eGFR>60ml/min/1.73m^2.[32] On the other hand, Lindeman et al.[33] reported that the mean decrease in creatinine clearance with aging was 0.75 ml/min/year, which smaller than the predicted value of CCr (1.0 ml/min/year). Thus, CCr tend to underestimate creatinine clearance of the elderly subjects. Actually, our data demonstrated that CCr was lower than eGFR above 70 years old and then, the inverse relationship was observed below 70 years old. Moreover, the value of CCr will vary greatly depending on body weight.[16] In the present study, the body weight was gradually decreased with lower classified category of CCr (Table 5). In contrast, the

overall analysis revealed that the high BMI which positively correlated with the CCr was one of the most important risks of the prevalence of AF in our study. Therefore, the lower category of CCr group was associated with the lower body weight and higher rate of woman, which might be low prevalence of AF.

Of note, CCr is an estimation of the creatinine clearance, but not of the GFR, and was suboptimal performance for GFR estimation, especially in advanced kidney disease which included tubular creatinine secretion.[34,35] Therefore, Levey et al.[36] published new formula based on patients who had a GFR<60ml/min/1.73m^2 from the Modification of Diet in Renal Disease (MDRD) study. The formula was found to be superior to the Cockcroft Gault formula for estimating GFR. However, the MDRD study was developed in mostly whites and African Americans. Matsuo et al.[37] reported that eGFR obtained using the isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation was significantly higher than measured GFR by inulin clearance in Japanese patients and calculated a correction coefficient

of 0.808 for the MDRD Study equation and developed a new Japanese equation for GFR estimation.

Although the best overall index of renal function is the GFR,[38] measuring GFR was cumbersome and taking a lot of time. eGFR is currently used by most clinical laboratories, that is reliable and convenient index for the diagnosis and evaluation of chronic kidney disease. The chronic kidney disease was staged by levels of eGFR according to the KDIGO clinical practice guideline of chronic kidney disease.[15] The eGFR was calculated by the adjustment of the standard body surface area (1.73m^2), and the value was apart from real value when the body weight or/and height deviated from standard value. However, there were almost equal in the mean body weight and height in the three classified category groups of eGFR in this study (Table 3). Thus, the odds ratio of the risk of having AF was significantly high risks at the lowest category of eGFR (≦59) compared with the highest category of eGFR (≧90) after adjustment of the age, gender, diabetes mellitus and smoking on the multivariate logistic regression analysis

(OR=2.10, CI: 1.21-3.86, Table 4). Recently, Ohyama et al.[39] also reported that eGFR≦59 ml/min/m^2 was strongly associated with prevalence of AF after adjustment of the age, gender, diabetes mellitus, smoking as well as hypertension and cardiac disease on the multivariate logistic regression analysis in the community-based population in Gunmma prefecture. The discrepancy of these results between our and above cited studies may be explained by the differences of age (56.5 vs. 53.2 years old), gender (male: 48.2% vs. 62.0%) and/or number of subjects (20,091 vs. 85,414), which have an effect on the prevalence of AF. Another possible reason is the prevalence of AF in high GFR group has too small (6/3,148 subjects, 0.19%) that is biased in the latter study compared with our study (44/15,491 subjects, 0.28%). In our study, eGFR but not CCr was significantly associated with prevalence of AF, which has been suggested in our country.[40,41] However, this significant association was disappeared after adjustment of the confounding variables such as cardiac disease and hypertension in the multivariate regression analysis. Thus, it was considered that these variables were closely

connected with eGFR

Atrial fibrillation and flutter were defined the AF in this study, because only 13 patients (1.3%) were diagnosed with atrial flutter by the automated computerized analysis. Moreover, atrial flutter and fibrillation sometimes coexist as they are the electrical consequence of the same arrhythmogenic substrate. The frequency of the coexistence of the two arrhythmias is not easily predictable because both arrhythmias are often silent. Randomized controlled trial of atrial fibrillation also included patients with atrial flutter.[42,43]

Limitations

Various limitations apply to the present study. Firstly, this was cross-sectional observation study. Thus, the mechanism between prevalence of AF and risk factors for AF was not known. Secondary, prevalence of AF was only defined by standard 12-lead electrocardiographic recording at one time. Almost of all paroxysmal AF was excluded in this study. Thirdly,

medical histories of risk factors for AF were only collected by the questionnaire at the annular healthy check-up, the actual medical history was difficult to correct in some cases, which might be limited and would have caused a bias in the results. Fourthly, some patients with medication were included in this cohort, may influence prevalence of AF. Lastly, the eGFR equation by the MDRD study was developed in mainly in CKD patients and the accuracy was still moderate particularly in the GFR>60ml/min/1.73m^2,[36] then eGFR is calculated to be lower value when the MDRD equation applied to healthy subjects. To improve this weak point, CKD-EPI formula using the different estimating equation by the value of serum creatinine has been devised in the United States.[44] However, the estimated error of the eGRF calculated by modified CKD-EPI formula was greater than that calculated by modified MDRD in Japanese subjects with GFR<60ml/min/1.73m^2.[45] Thus, the eGFR calculated by CKD-EPI formula is not suitable for the Japanese subjects at present time.

Conclusion

The prevalence of atrial fibrillation actually rises with increasing aging population in living in the middle part of Japan. Cardiac disease, gender, aging, hyperlipidemia, obesity, hypertension especially in systolic blood pressure and renal dysfunction were strong risk factors for prevalence of AF. The evaluation of renal dysfunction as a morbidity risk of atrial fibrillation was suggested that eGFR should be used instead of CCr (Cockcroft-Gault formula) in general population in this area.

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FIGURE LEGENDS

Figure 1. Correlation between CCr, eGFR and age.

eGFR: estimated glomerular filtration rate, CCr: creatinine clearance (Cockcroft-Gault formula), min: minutes,

Red color was correlation line and 95% confidential interval of CCr.

Blue color was correlation line and 95% confidential interval of eGFR.

Supplementary Figure 1. Correlation between eGFR, CCr and bpdy mass index (BMI)

eGFR: estimated glomerular filtration rate, CCr: creatinine clearance (Cockcroft-Gault formula), min: minutes,