Doctor of Medicine

Metabolic Syndrome and the Risk of New-Onset Atrial Fibrillation in Middle-Aged East Asian Men

The Graduate School

of the University of Ulsan

Department of Medicine

Yong-Giun Kim

Metabolic Syndrome and the Risk of New-Onset Atrial Fibrillation in Middle-Aged East Asian Men

Supervisor : Kee-Joon Choi

A Dissertation

Submitted to

the Graduate School of the University of Ulsan

in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Medicine

by

Yong-Giun Kim

Department of Medicine

Ulsan, Korea

February 2018

Metabolic Syndrome and the Risk of New-Onset Atrial Fibrillation in Middle-Aged East Asian Men

This certifies that the dissertation of Yong-Giun Kim is approved.

Jun Kim
Committee Chair Dr.

Kee-Joon Choi
Committee Member Dr.

Gi-Byoung Nam
Committee Member Dr.

Jong-Min Song
Committee Member Dr.

Young Keun On
Committee Member Dr.

Department of Medicine
Ulsan, Korea
February 2018

English Abstract

Metabolic Syndrome and the Risk of New-Onset Atrial Fibrillation in Middle-Aged East Asian Men

Division of Cardiology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

Yong-Giun Kim

Background: The components of metabolic syndrome have been implicated in the development of atrial fibrillation (AF). Although the prevalence of AF has been increasing in East Asia, the association between metabolic syndrome and AF is uncertain. This study aimed to determine the association between metabolic syndrome and AF in middle-aged East Asian men.

Methods: A total of 24,741 middle-aged Korean men without baseline AF were enrolled in a health screening program from January 2003 to December 2008. Among them, 21,981 subjects were evaluated to determine the risk of AF based on baseline metabolic syndrome status through December 2016. At every visit, the subjects were evaluated for AF using electrocardiography. Metabolic syndrome was defined using the criteria of the International Diabetes Federation.

Results: Metabolic syndrome was present in 2,529 subjects (11.5 %). Mean (± standard deviation) age was 45.9 ± 5.3 years. During a mean follow-up of 8.7 years, 168 subjects (0.8%) were diagnosed with AF. The age-adjusted and multivariate-adjusted hazard ratios (HR) for metabolic syndrome with AF were 1.62 (95% confidence interval [CI] 1.08-2.44, p=0.02) and 1.57 (95% CI 1.04-2.38, p=0.03), respectively. Among the components of metabolic syndrome, central obesity (age-adjusted HR 1.62, 95% CI 1.14-2.29, p<0.01) and raised blood pressure (age-adjusted HR 1.43, 95% CI 1.05-1.94, p=0.02) were associated with an increased risk of AF.

Conclusions: Metabolic syndrome is associated with an increased risk of AF in middle-aged East Asian men. Of the components of metabolic syndrome, central obesity is the most potent risk factor for the development of AF in this population.

Key words: atrial fibrillation; metabolic syndrome; central obesity; risk factor

Contents

Lists of tables and figures

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia requiring treatment in clinical practice, and is associated with increased mortality.[1, 2] Although the prevalence of AF has been known to be higher in the West than in Asia, the prevalence in Asia has been increasing with aging populations and a westernized lifestyle. In South Korea, prevalence rates of AF progressively increased 2.69-fold between 2004 and 2013.[3]

Metabolic syndrome is a cluster of characteristics including central obesity (defined as waist circumference [WC] with ethnicity specific values), hypertension (HTN), diabetes mellitus (DM), and dyslipidemia which are recognized as risk factors for cardiovascular disease; its prevalence has increased globally.[4-6] In addition, previous studies suggest that metabolic syndrome is associated with an increased risk of AF.[7-9] However, previous studies were aimed at western populations, or the definition of metabolic syndrome was not exact (Body mass index [BMI] used in place of WC, for example). BMI has a limitation for replacement of central obesity because Asians have a lower BMI in general at a given central obesity compared with Europeans.[10]

In this study, we aimed to determine the association of metabolic syndrome with the risk of new onset AF in middle-aged East Asian men.

METHODS

Study Population

We conducted a retrospective cohort study using data from 21,981 individuals who participated in an annual or biennial comprehensive health screening program at Ulsan University Hospital, Ulsan, Republic of Korea, from January 2003 to December 2008 (**Figure 1**).

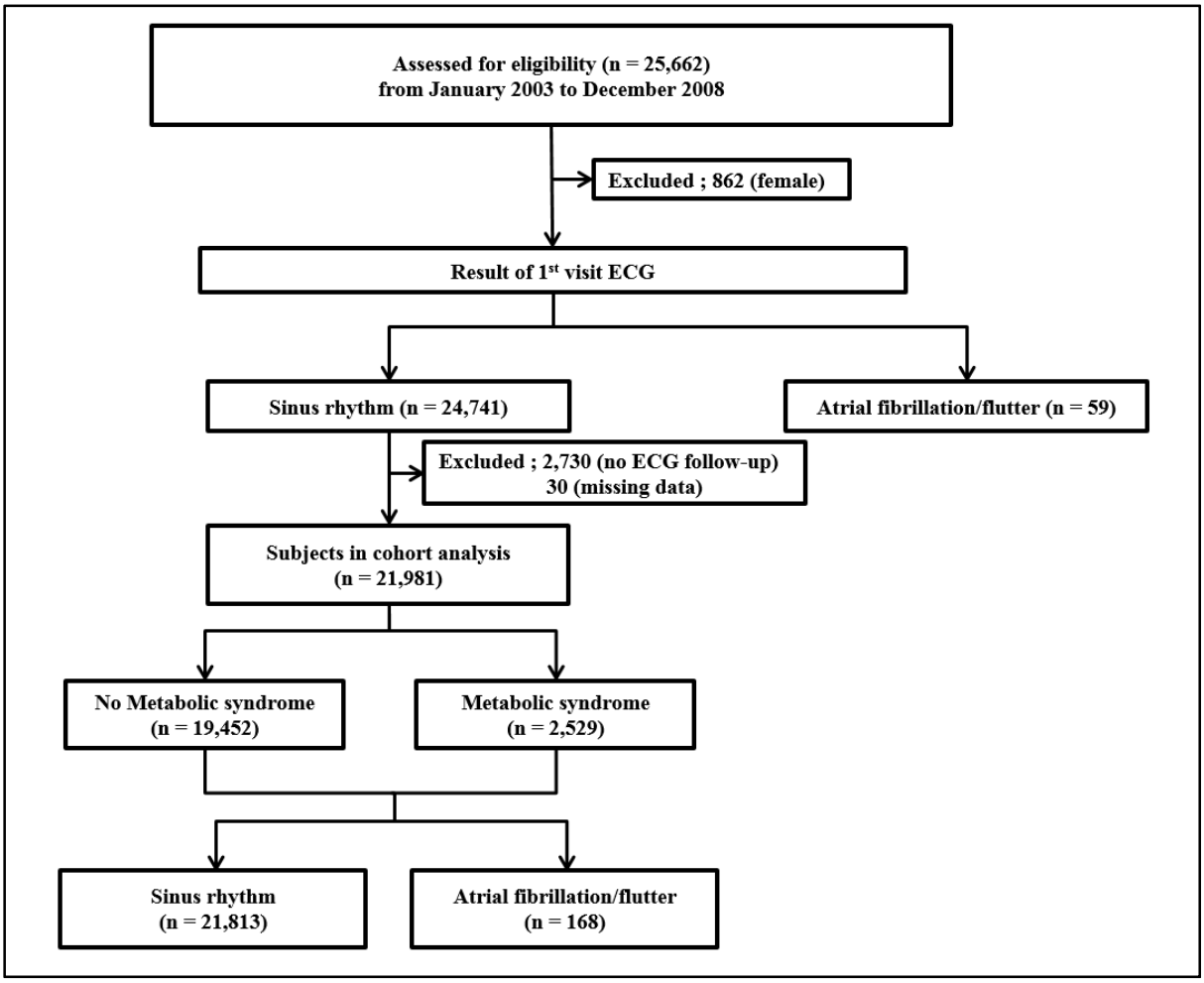

Figure 1. Diagram of the study.

The Korean Industrial Safety and Health Law require working individuals to participate in an annual or biennial health examination. In addition to mandatory health examination, health screening program of Ulsan University Hospital included a 12-lead electrocardiography (ECG). Most of the individuals who participated in the health examination at our center were employees of heavy industries and most of them were men (n=24,800, 97%); Women (n=862) were excluded. In addition, we excluded subjects if they did not have an initial ECG, if they had an AF or atrial flutter (AFL) on the initial ECG, if they did not have a follow-up ECG, or if data of questionnaires and the others were unavailable. AF and AFL were diagnosed from the 12-lead ECG recoded at a follow-up visit (annual or biennial). AFL was included as an end-point, as it is closely related to AF, often coexists with AF, and is associated with a similar risk of stroke.[11-13] The study protocol was approved by the Institutional Review Board at Ulsan University Hospital (IRB No. 2017-02-023). Information of subjects were anonymized and de-identified prior to analysis. The requirement for informed consent was waived because of the anonymity of the subjects and the nonintrusive nature of the study.

Data collection

Data was collected using the Electronic Medical Recording system of Ulsan University Hospital. Anthropometric measurements were made of the individuals while wearing light clothing and without shoes by well-trained examiners. Height was measure to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI values were calculated by dividing weight (kg) by height squared (m^2). WC was measured in the standing position, midway between the lowest rib and the iliac crest with a measuring tape. Blood pressure was measured by well-trained nurses using a mercury sphygmomanometer in the sitting position after at least a 10 minutes rest period. Following an overnight fasting (at least 8-hours), blood samples were collected analyzed in the same core clinical laboratory, which has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Blood tests included fasting glucose; hemoglobin A1c (HbA1c); a fasting plasma lipid profile including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglycerides (TG); serum creatinine; and blood urea nitrogen.

Estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease equation (eGFR = 175 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$). Data on smoking status (never, former, or current); alcohol drinking status (frequency, amount); frequency of exercise; and medical history were collected from self-administered questionnaires. HTN was defined as a systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90mmHg or current use of antihypertensive medication. DM was defined as fasting serum glucose value ≥ 126 mg/dL, HbA1c ≥ 6.5% or the use of blood glucose lowering agents. Chronic kidney disease was defined as eGFR < 60ml/min/1.73m^2.

Definition of metabolic syndrome

Metabolic syndrome was defined according to the criteria of the International Diabetes Federation.[14] Central obesity (WC ≥ 90 cm) had to be present and any 2 of the following 4 components are required: 1) Raised blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or treatment of previously diagnosed HTN); 2) Raised fasting plasma glucose (≥ 100 mg/dL or diagnosed type 2 diabetes); 3) Raised TG (≥ 150 mg/dL or drug treatment for high TG); 4) Reduced HDL-C (< 40 mg/dL or drug treatment for low HDL-C).

Statistical analysis

All baseline patient characteristics were summarized as mean ± standard deviation (SD) or frequency (percentage) for continuous or categorical variables. The Baseline characteristics by baseline metabolic syndrome status were compared by the chi-square test and Student's *t* test for categorical and continuous variables, respectively. Follow-up years were computed from the baseline examination until a first AF or AFL diagnosis, loss to follow-up, or the end date of December 2016. We estimated the cumulative incidence of AF based on the Kaplan-Meier method and we compared the cumulative incidence rates curves by the log-rank test. Overall and age-adjusted incidence rates for AF by the baseline metabolic syndrome status were also calculated. Age-adjusted and multivariate-adjusted hazard ratios (HRs) of the metabolic syndrome were estimated by using the Cox

proportional hazard regression model. Multivariate-adjustments were made for age, smoking status, regular exercise (≥1 time/week), alcohol drinking status, and chronic kidney disease. HRs for individual components of metabolic syndrome after additional adjustment for the other components were also evaluated by Cox model. Results of the Cox proportional hazard model were presented as the hazard ratio (HR) and the 95% confidence interval (95% CI). Analyses were performed with the use of R software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All reported *p*-values are two-sided, and *p*-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 21,981 men were enrolled in the cohort analysis. The mean age was 45.9±5.3 years. At baseline, metabolic syndrome was present in 2,529 subjects (11.5 %). **Table 1** shows the baseline characteristics of this study population by baseline metabolic syndrome status. Subjects with metabolic syndrome were older, and had higher values for BMI, WC, SBP, DBP, pulse pressure, and had more comorbidities than subjects without metabolic syndrome.

Table 1. Baseline characteristics by baseline metabolic syndrome status

Variable	No metabolic syndrome (n=19,452)	Metabolic syndrome (n=2,529)	*p* value
Age (years)	45.9±5.2	46.0±5.7	0.03
BMI (kg/m^2)	23.2±2.3	27.0±2.1	<0.01
Waist circumference (cm)	82.2±6.1	94.1±4.0	<0.01
Systolic blood pressure (mmHg)	119.5±13.9	128.7±14.5	<0.01
Diastolic blood pressure (mmHg)	77.0±9.6	83.3±10.0	<0.01
Pulse pressure (mmHg)	42.6±8.1	45.4±8.7	<0.01
Hypertension (%)	3554 (18.3)	1096 (43.3)	<0.01
Diabetes mellitus (%)	1648 (8.5)	422 (16.7)	<0.01
Stroke (%)	65 (0.3)	5 (0.2)	0.35
Smoking status (%)			0.02
Never smoker	6300 (32.7)	752 (30)	
Former smoker	4898 (25.4)	644 (25.7)	
Current smoker	8083 (41.9)	1113 (44.4)	
Regular exercise (%)[a]	12972 (67.0)	1755 (69.7)	0.01
Alcohol drinking status (%)			<0.01
<40g/day	18732 (96.5)	2387 (94.5)	
≥40g/day	670 (3.5)	138 (5.5)	
Glucose (mg/dL)	100.1±15.6	108.5±20.3	<0.01
HbA1c (%)	5.29±0.62	5.56±0.76	<0.01
Total cholesterol (mg/dL)	194.6±32.5	204.8±34.0	<0.01
Triglyceride (mg/dL)	124.1±73.2	197.0±104.5	<0.01
LDL-C (mg/dL)	121.7±29.9	124.2±33.1	<0.01

Table 1. Continued

HDL-C (mg/dL)	48.0±11.1	41.3±8.8	<0.01
BUN (mg/dL)	15.7±3.9	15.5±3.6	0.05
Creatinine (mg/dL)	1.09±0.16	1.12±0.14	<0.01
GFR (mL/min/1.73m^2)	74.1±9.9	72.0±10.3	<0.01
Chronic kidney disease	975 (5.0)	233 (9.2)	<0.01

Data are reported as mean ± SD or as number (%).

BMI = body mass index; BUN = blood urea nitrogen; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol.

[a]≥1 time/week.

Table 2 shows the prevalence of metabolic syndrome and the individual components of metabolic syndrome.

Table 2. Prevalence of metabolic syndrome and individual components of metabolic syndrome

	Number (%)
Metabolic syndrome	2529 (11.5)
Metabolic syndrome components	
Central obesity	4018 (18.3)
Raised blood pressure	7789 (35.4)
Raised fasting plasma glucose	10503 (47.7)
Raised triglycerides	6524 (29.7)
Reduced HDL-C	5653 (25.7)

HDL-C = high density lipoprotein cholesterol.

During a mean follow-up of 8.7 years, AF (including AFL) occurred in 168 subjects (0.8%, AF = 166, AFL = 2). **Figure 2** depicts the cumulative incidence rates of AF by baseline metabolic syndrome status. Although overall AF incidence rates were low (8.81/10,000 person-years), AF incidence rates were higher in subjects with metabolic syndrome (13.32/10,000 person-years) than in subjects without metabolic syndrome (8.25/10,000 person-years). This trend was consistently observed after age-adjustment. The age-adjusted AF incidence rates were 5.94 and 4.29/10,000 person-years in subjects with and without metabolic syndrome, respectively (**Table 3**).

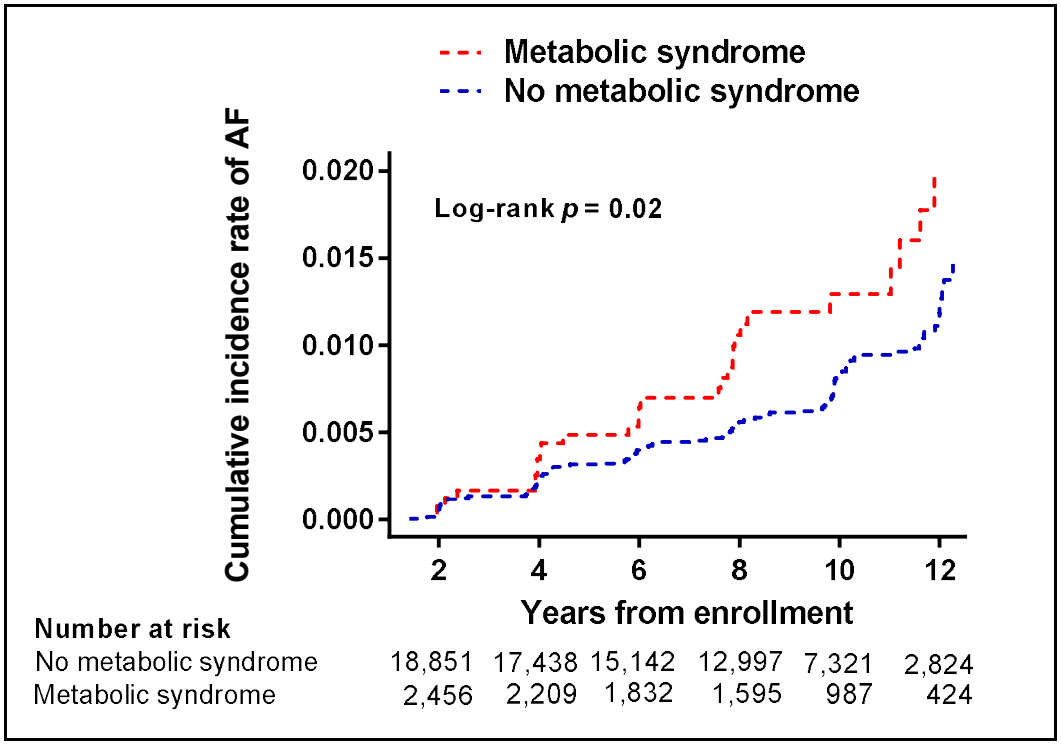

Figure 2. Cumulative incidence rates of atrial fibrillation by baseline metabolic syndrome status.

Table 3. Incidence rates of atrial fibrillation according to metabolic syndrome status

	No metabolic syndrome (n=19,452)	**Metabolic syndrome (n=2,529)**
Number of events	140	28
Person-years	169729	21019
Incidence rate (10,000 person-years)	8.25	13.32
Age-adjusted incidence rates (10,000 person-years)	4.29	5.94

As seen in **Table 4**, metabolic syndrome was associated with an increased risk of AF. In the Cox proportional hazard regression model, the age-adjusted HR for AF in subjects with metabolic syndrome was 1.62 (95% CI 1.08-2.44, p=0.02). In multivariate models adjusted for age, smoking status, regular exercise, drinking status, and chronic kidney disease, the HR for AF in subjects with metabolic syndrome was 1.57 (95% CI 1.04-2.38, p=0.03). Among the components of metabolic syndrome, central obesity (HR 1.62, 95% CI 1.14-2.29, p<0.01) and raised blood pressure (HR 1.43, 95% CI 1.05-1.94, p=0.02) were associated with an increased risk of AF in the age-adjusted model. However, central obesity (HR 1.62, 95% CI 1.13-2.33, p<0.01) was the only statistically significant risk factor after multivariate adjustment (**Table 4**). Other variables that were adjusted for the multivariate analysis did not have a statistically significant association with AF, except age (HR 1.72, 95% CI 1.39-2.11, p<0.01, for a 1-SD increment).

Table 4. Risk of atrial fibrillation according to metabolic syndrome status and individual components of metabolic syndrome: age- and multivariate-adjusted models

	Age-adjusted HR (95% CI)	*p* value	Multivariate-adjusted HR (95% CI)	*p* value
Metabolic syndrome[a]	1.62 (1.08-2.44)	0.02	1.57 (1.04-2.38)	0.03
Components of metabolic syndrome[b]				
Central obesity	1.62 (1.14-2.29)	<0.01	1.62 (1.13-2.33)	<0.01
Raised blood pressure	1.43 (1.05-1.94)	0.02	1.35 (0.99-1.86)	0.06
Raised fasting plasma glucose	1.16 (0.85-1.57)	0.35	1.05 (0.77-1.44)	0.75
Raised triglycerides	0.84 (0.60-1.19)	0.33	0.71 (0.49-1.02)	0.7
Reduced HDL-C	1.04 (0.74-1.47)	0.81	1.06 (0.74-1.53)	0.74

Cox proportional hazard models were used to estimate HR and 95% CI.

CI = confidence interval; HDL-C = high density lipoprotein cholesterol; HR = hazard ratio.

[a]Multivariate-adjusted HR = adjusted for age, smoking status, regular exercise, alcohol drinking status, and chronic kidney disease.

[b]Multivariate-adjusted HR = adjusted for age, smoking status, regular exercise, alcohol drinking status, chronic kidney disease, and other components of metabolic syndrome.

DISCUSSION

In the present study, we have shown that middle-aged East Asian men with metabolic syndrome had a 57% increased risk for the development of AF during a mean follow-up of 8.7 years. Among the components of metabolic syndrome, central obesity was the strongest predictor for the development of AF. Other components of metabolic syndrome were not significantly associated with an increased risk of AF.

Metabolic syndrome is a cluster of risk factors for cardiovascular disease and each individual component has been suggested as having a relationship with an increased risk of AF. However, the exact mechanism for a relationship between metabolic syndrome and AF is not well established. Several studies have reported that metabolic syndrome is associated with AF.[7-9, 15)] A prospective, large observational cohort study based on health examinations in a Japanese population reported that metabolic syndrome, according to the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel[16)], was associated with an increased risk of AF (age and gender-adjusted HR 1.88). In addition, components of metabolic syndrome were also associated with an increased risk of AF (age and gender-adjusted HR of obesity, elevated blood pressure, low HDL-C, and impaired fasting glucose were 1.64, 1.69, 1.52, and 1.4, respectively); the only exception was elevated triglycerides.[7)] Other studies of western populations also revealed that metabolic syndrome was a risk factor for AF (HR 1.20~1.67).[8, 15)]

Our results are consistent with previous studies, although the definition of metabolic syndrome is different. We found that metabolic syndrome is associated with an increased risk of AF (HR 1.57). We also found an increased risk of AF associated with central obesity, which is known to be a factor for increased risk.[8, 15)] Several mechanisms have been proposed to explain the association between obesity and AF. There is a direct correlation between obesity and left atrial size and increased left atrial size is an important precursor of AF due to left atrial remodeling.[17, 18)] In addition, obesity-related oxidative stress, inflammation,[19-21)] neurohormonal activation,[22)] and obstructive sleep apnea[23, 24)] could facilitate the development of AF. Central obesity is the essential risk factor for the diagnosis of metabolic syndrome, and is regarded as an early step in the etiological cascade leading to full

metabolic syndrome.[25] Although mean BMI is lower in Asian population than in non-Asian population, Asian populations tend to have more central obesity at a given BMI. Therefore, central obesity could provide more predictive information for the development of AF in Asian populations. Previous Asian studies revealed that central obesity is more significant risk factor for AF compare to general obesity (by BMI)[26] and increases the risk of AF regardless of BMI except for obese group (BMI > 30 kg/m^2).[27]

Unlike previous studies,[7, 8, 15] however, we found that other components of metabolic syndrome are not associated with development of AF. HTN is a well-established risk factor for AF.[28, 29] Raised blood pressure, one of the components of metabolic syndrome, is not identical to HTN. This also included blood pressure values that were lower, as compared with HTN, which could explain why raised blood pressure was not statistically significant after the multivariate-adjusted analysis (HR 1.35, p=0.06) in this study. Type 2 DM[30-32] and reduced HDL-C[33] have also been questioned as risk factors for AF, especially in men. Raised TG was not associated with an increased risk of AF in previous studies.[7, 8, 15, 33] The incidence of AF and the prevalence of metabolic syndrome in our study were lower than previous studies.[7-9] This could be explained by ethnic differences, age, or the occupation of the study populations. Most of the subjects in our study were manual laborers.

The strengths of our study are the large sample size and the well-organized cohort design characterized by consistent follow-up due to the very low turnover rates in employment, the long average length of service (over 18 years), and the obligation for health examinations, including ECGs (at least once every 2 years). Another advantage of our study is that AF was identified purely by 12-lead ECG, not by a self-reported questionnaire or code defined by the International Classification of Disease.

This study had several limitations. First, this study was a retrospective cohort study with inherent limitations. Second, information regarding smoking, exercise, alcohol intake, and medical history were self-administered, thus allowing for recall bias. Third, the study population may not be representative of the general population because all subjects were working individuals and middle-aged men. However, this is also a strength of our study because there are few data regarding middle-

aged men. AF constitutes a significant economic burden worldwide.[34, 35] From an economic standpoint, prevention of AF in this group is important because middle-aged men are the main agents of economic activity. Finally, the diagnosis of AF was based only on annual or biennial 12-lead ECGs. So, the diagnosis of AF, especially paroxysmal AF, may have been underestimated.

CONCLUSION

This large and long-term follow-up cohort study demonstrated that metabolic syndrome is associated with an increased risk of AF in middle-aged East Asian men. Among the components of metabolic syndrome, central obesity is the most potent risk factor for the development of AF. These finding suggest that strategies to reduce the development of metabolic syndrome, especially central obesity, might reduce the risk of AF in middle-aged East Asian men.

REFERENCES

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98(10):946-52.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37(38):2893-962.
3. Lee H, Kim TH, Baek YS, Uhm JS, Pak HN, Lee MH, et al. The Trends of Atrial Fibrillation-Related Hospital Visit and Cost, Treatment Pattern and Mortality in Korea: 10-Year Nationwide Sample Cohort Data. Korean Circ J 2017;47(1):56-64.
4. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 2005;28(11):2745-9.
5. Lim S, Shin H, Song JH, Kwak SH, Kang SM, Won Yoon J, et al. Increasing prevalence of metabolic syndrome in Korea: the Korean National Health and Nutrition Examination Survey for 1998-2007. Diabetes Care 2011;34(6):1323-8.
6. Batsis JA, Nieto-Martinez RE, Lopez-Jimenez F. Metabolic syndrome: from global epidemiology to individualized medicine. Clin Pharmacol Ther 2007;82(5):509-24.
7. Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. Circulation 2008;117(10):1255-60.
8. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2010;159(5):850-6.
9. Nystrom PK, Carlsson AC, Leander K, de Faire U, Hellenius ML, Gigante B. Obesity, metabolic syndrome and risk of atrial fibrillation: a Swedish, prospective cohort study. PLoS One 2015;10(5):e0127111.
10. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363(9403):157-63.

11. Tunick PA, McElhinney L, Mitchell T, Kronzon I. The alternation between atrial flutter and atrial fibrillation. Chest 1992;101(1):34-6.

12. Ellis K, Wazni O, Marrouche N, Martin D, Gillinov M, McCarthy P, et al. Incidence of atrial fibrillation post-cavotricuspid isthmus ablation in patients with typical atrial flutter: left-atrial size as an independent predictor of atrial fibrillation recurrence. J Cardiovasc Electrophysiol 2007;18(8):799-802.

13. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64(21):e1-76.

14. IDF worldwide definition of the metabolic syndrome. International Diabetes Federation Web site. http://www.idf.org/metabolic-syndrome Accessed December 12, 2016.

15. Tanner RM, Baber U, Carson AP, Voeks J, Brown TM, Soliman EZ, et al. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). Am J Cardiol 2011;108(2):227-32.

16. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-97.

17. Wang TJ, Parise H, Levy D, D'Agostino RB, Sr., Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292(20):2471-7.

18. Ayer JG, Almafragy HS, Patel AA, Hellyer RL, Celermajer DS. Body mass index is an independent determinant of left atrial size. Heart Lung Circ 2008;17(1):19-24.

19. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282(22):2131-5.

20. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol

2012;60(22):2263-70.

21. Hajhosseiny R, Matthews GK, Lip GY. Metabolic syndrome, atrial fibrillation, and stroke: Tackling an emerging epidemic. Heart Rhythm 2015;12(11):2332-43.

22. Sarzani R, Salvi F, Dessi-Fulgheri P, Rappelli A. Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. J Hypertens 2008;26(5):831-43.

23. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110(4):364-7.

24. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol 2007;49(5):565-71.

25. Alberti KG, Zimmet P, Shaw J, Group IDFETFC. The metabolic syndrome--a new worldwide definition. Lancet 2005;366(9491):1059-62.

26. Zhang X, Zhang S, Li Y, Detrano RC, Chen K, Li X, et al. Association of obesity and atrial fibrillation among middle-aged and elderly Chinese. Int J Obes 2009;33(11):1318-25.

27. Baek YS, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, et al. Associations of Abdominal Obesity and New-Onset Atrial Fibrillation in the General Population. J Am Heart Assoc 2017;6(6).

28. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98(5):476-84.

29. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373(9665):739-45.

30. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol 2002;55(4):358-63.

31. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care 2009;32(10):1851-6.

32. Fontes JD, Lyass A, Massaro JM, Rienstra M, Dallmeier D, Schnabel RB, et al. Insulin resistance and atrial fibrillation (from the Framingham Heart Study). Am J Cardiol 2012;109(1):87-90.

33. Watanabe H, Tanabe N, Yagihara N, Watanabe T, Aizawa Y, Kodama M. Association between lipid profile and risk of atrial fibrillation. Circ J 2011;75(12):2767-74.

34. Ringborg A, Nieuwlaat R, Lindgren P, Jonsson B, Fidan D, Maggioni AP, et al. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Europace 2008;10(4):403-11.

35. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129(8):837-47.

국문요약

연구목적: 대사증후군의 구성요소들은 심방세동의 발생과 연루되어 있는 것으로 알려져 있다. 동아시아에서 심방세동의 유병률은 증가하고 있지만 대사증후군과 심방세동의 연관성에 대해서는 아직까지 잘 알려져 있지 않다. 본 연구에서는 동아시아 중년 남성에서 대사증후군과 심방세동의 연관성에 대해 알아보고자 한다.

연구방법: 2003 년부터 2008 년까지 울산대학교병원 건강검진센터에서 건강검진을 받았으며, 초회 건강검진에서 심방세동이 관찰되지 않은 총 24,741 명의 중년 남성을 추출 하였다. 이 중 추후 건강검진을 받았으며, 손실자료가 없는 총 21,981 명을 대상으로 2016 년까지의 기간 동안 대사증후군과 심방세동 위험성과의 관계에 대해 연구를 진행하였다. 매회 방문 시 마다 심전도를 이용하여 심방세동 유무에 대해 평가하였다. 대사증후군의 정의는 International Diabetes Federation 의 기준에 따랐다.

연구결과: 대사증후군은 총 2,529 명 (11.5%)의 연구대상자에서 관찰되었다. 평균 연령은 45.9 세 였다. 평균 추적관찰 기간은 8.7 년 이였으며, 총 168 명 (0.8%)의 연구대상자에서 심방세동이 새롭게 발생하였다. 연령 및 다변량변수 보정 분석에서 대사증후군이 있는 경우는 없는 경우에 비하여 심방세동 발생 위험도 (HR: Hazard ratio)가 각각 1.62 (95% 신뢰구간 1.08-2.44, p=0.02), 1.57 (95% 신뢰구간 1.04-2.38, p=0.03) 이였다. 대사증후군의 구성요소들 중 연령보정 분석 상 심방세동 발생 위험이 유의하게 증가한 항목은 복부비만 (HR 1.62, 95% 신뢰구간 1.14-2.29, p<0.01)과 혈압 상승 (HR 1.43, 95% 신뢰구간 1.05-1.94, p=0.02) 이였다.

결론: 대사증후군은 동아시아 중년 남성에서 심방세동의 위험성 증가와 관련이 있다. 대사증후군의 구성요소들 중, 복부비만은 이 인구집단에서 가장 강력한 심방세동의 위험 인자이다.

중심단어: 심방세동, 대사증후군, 복부비만, 위험인자