Risk of Atrial Fibrillation in Relation to the Time Course of Type 2 Diabetes Mellitus and Fasting Blood Glucose

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The relation of progression of type 2 diabetes and detailed fasting glucose level with risk of atrial fibrillation (AF) is not well known. A total of 6,199,629 subjects not diagnosed with AF who underwent health check-up in 2009 were included from the Korean National Health Insurance Service database. Risk of AF was compared among subjects with normal fasting glucose (NFG), subjects with impaired fasting glucose (IFG), patients with diabetes duration <5 years (early diabetes mellitus [DM]), and patients with diabetes duration ≥5 years (late DM). Next, risk of AF stratified by fasting glucose level per 10 mg/dL was assessed. During a mean follow-up of 7.2 years, the risk of AF significantly increased across the time course of type 2 diabetes (adjusted hazard ratio (aHR) 1.04, 95% confidence interval (CI) 1.02 to 1.05 for IFG; aHR 1.06, 95% CI 1.04 to 1.08 for early DM; aHR 1.09, 95% CI 1.07 to 1.11 for late DM). The risk of AF was significantly higher in subjects who progressed to type 2 diabetes in the IFG group. Risk of AF increased with a 10 mg/dL increment of fasting blood glucose (p-for-trend <0.0001). However, there was a U-shape relationship between fasting blood glucose and risk of AF in those who received antidiabetic medication. In conclusion, the risk of AF increased with the time course of type 2 diabetes. However, low blood glucose in antidiabetic medication user was associated with an increased risk of AF. **(Am J Cardiol 2019;124:1881−1888)**

Atrial fibrillation (AF) is a well-known risk factor of cardiovascular disease, ischemic stroke, and mortality.[1] Modifiable risk factors for AF development have been proposed.[2,3] Impaired fasting glucose (IFG) as well as type 2 diabetes was reportedly associated with increased risk of AF development,[4,5] underscoring that hyperglycemia should also be considered to be a risk factor of incident AF. After the development of type 2 diabetes, a microvascular complication of type 2 diabetes was significantly associated with incident AF,[6] and the duration of treated type 2 diabetes correlated with the risk of AF.[7] Therefore, it is important to stratify the risk of AF development in patients with type 2 diabetes. However, the risk of AF development according to the serial time course of type 2 diabetes has rarely been reported. We aimed to investigate the association of the overall time course of type 2 diabetes with the risk of AF. Furthermore, we sought to investigate the relationship between glucose levels and the risk of AF.

Methods

This study used data from the National Health Insurance Service (NHIS) of Korea. The NHIS is an obligatory system of national health insurance covered by the Korean government which has provided extensive medical care to 97% of Koreans. The other 3% with low incomes are supported by the Medical Aid Program, which has been incorporated into an NHIS database. Thus, the data from the claims database of the NHIS covers the entire Korean population. The database comprises demographics, diagnoses, prescriptions, medical procedures, the records of inpatient and outpatient services, and information about death. Recorded diagnoses are based on the *International Classification of Disease-10th Revision-Clinical Modification* (ICD-10-CM) codes. The NHIS provides national health examinations biennially to all those covered by insurance. This examination includes body mass index (BMI), waist circumference, and a subset of laboratory tests, including fasting blood glucose, blood pressure, lipid profile, liver enzymes, urinalysis, and estimated glomerular filtration rate. In addition, a self-reported questionnaire, including smoking, alcohol consumption, and physical activity is completed. This study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. E-1901-089-1004). The committee waived informed consent because the data used in this analysis was anonymized. This study was performed following the ethical guidelines of the Declaration of Helsinki of 1975.

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Of the 6,330,369 subjects aged ≥20 years who underwent the national health examination between January 2009 and December 2009, a total of 6,199,629 subjects were finally included in the study after excluding 104,305 patients who had been diagnosed with AF before the index national health examination, and 26,435 patients who were newly diagnosed with AF within 1 year from index national health examination to avoid the potential surveillance bias (Supplementary Figure 1). Type 2 diabetes was defined based on the laboratory findings of the index health examination (≥126 mg/dL of fasting blood glucose) or ICD-10-CM diagnostic codes (E11−E14) and the prescription of antidiabetic drugs (oral hypoglycemic agents and insulin). We divided the study population into 4 groups according to the time course of type 2 diabetes: (1) normal fasting glucose (NFG), defined as subjects with <100 mg/dL of fasting blood glucose at the index health examination and no previous history of type 2 diabetes; (2) impaired fasting glucose (IFG), defined as subjects with ≥100 mg/dL and <126 mg/dL of fasting blood glucose at index health examination and no previous history of type 2 diabetes; (3) early diabetes mellitus (DM), subjects who were diagnosed as type 2 diabetes <5 years after the index health examination; and (4) late DM, subjects who diagnosed as type 2 diabetes ≥5 years after the index health examination. IFG was defined according to the 2003 guidelines of the American Diabetes Association.[8] We compared the risk of AF with the development of type 2 diabetes in subjects with IFG to clarify association of the time course of diabetes and AF risk. Next, we investigated the association of fasting blood glucose with risk of AF according to the use of antidiabetic medication in the entire population of 6,199,629 subjects. We further analyzed the association of fasting blood glucose with risk of AF according to type of antidiabetic medication among subjects who received antidiabetic medication.

We defined the entry of each participant into the study as the date of the index national health examination. The primary endpoint was incident AF based on ICD-10-CM diagnostic codes (I480-484, I489) during the follow-up period with hospitalization or ≥2 visits at an outpatient clinic from January 2009 to December 2017. We excluded the subjects without incident AF at the time of death or end of follow-up. Age, sex, BMI, current smoking, drinking ≥30 g alcohol per day, lower income (lowest 20 percentile), regular exercise, which was defined as over 5 times of moderate intensity exercise per week or over 3 times of vigorous intensity per week as per the supplied questionnaire, the incidence of hypertension, and dyslipidemia were regarded as covariates. Hypertension was defined as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at the index national health examination or ICD-10-CM diagnostic codes (I10-I13, I15) with the prescription of antihypertensive drugs. Dyslipidemia was defined as total cholesterol ≥240 mg/dL or ICD-10-CM diagnostic code (E78). Detailed definition of covariates and endpoints are summarized in Supplementary Table 1.

Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies and percentages. We used the Student's *t* test or Wilcoxon rank sum test to compare continuous variables based on the distribution and the Chi-square test to compare categorical variables. Incident rates of primary endpoints were calculated by dividing the number of events by the follow-up period of each subject and were expressed as per 1000 person-years. For the endpoint analysis, we used Cox proportional hazard regression analysis to evaluate the risk of endpoints according to the time course of type 2 diabetes. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from unadjusted and covariate-adjusted models. We performed subgroup analysis according to age (≥ 65 years), sex, current smoking, drinking ≥30 g per day, lower income (lowest 20 percentile), the presence of hypertension, and dyslipidemia. Cumulative incidence of AF according to the time course of type 2 diabetes was estimated by using the Kaplan-Meier curves. Differences among the 4 groups were compared by using the log-rank test. Because age is one of the most important factors in development of AF, we additionally analyzed the cumulative incidence rate according to time course of type 2 diabetes categorized by 3 age groups (20 to 39 years, 40 to 64 years, and ≥ 65 years) separately. The risk of incident AF adjusted for covariates was calculated for the 10 groups stratified by an increment of 10 mg/dL from <80 mg/dL to ≥160 mg/dL of fasting blood glucose at the index national health examination. For the assessment of the linear trend of hazard ratio, the ordinal terms of 10 groups were treated as continuous variables. The p-value was two-tailed, and a p-value <0.05 was considered statistically significant. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Results

The baseline characteristics of 6,199,629 study participants according to 4 groups are shown in Table 1. The mean age of the total population was 47.9 years, of which 56.4% were males. During the mean follow-up of 7.2 years, 127,268 (2.1%) incident AF occurred (an incidence rate 2.85 per 1,000 person-years). The differences in baseline characteristics of patients based on incident AF are summarized in Table 1.

The incidence of AF increased significantly across the NFG, IFG, early DM, and late DM groups (2.3, 3.4, 4.7, and 6.3 per 1000 person-years, respectively, p-for-trend <0.0001). Cumulative incidence was the highest in the late DM group, followed by the early DM, IFG, and NFG groups during the entire follow-up period (log-rank p <0.0001, Figure 1). When categorized by age group, the difference in cumulative incidence was apparent particularly in those <65 years old (Supplemental Figure 2). With NFG as a reference group, the risk for incident AF increased significantly across the time course of type 2 diabetes even after adjustment for covariate (p-for-trend <0.0001, Table 2). Among 1,402,179 subjects with IFG, 218,743 (15.6%) subjects progressed to type 2 diabetes during follow-up (an incidence rate of 20.27 per 1,000 person-years). Those who developed type 2 diabetes had a significantly higher risk of AF than those who did not in the IFG group (Supplementary Table 2). In the subgroup analysis according to demographic factors and co-morbidities, the trend of increase in incidence of AF with time course of type 2 diabetes was consistently observed in all subgroups except the group ≥65 years old (Table 3). In this group, the incidence of AF did not increase in relation to the duration of diabetes. Regarding the risk of AF development after covariate

Table 1
Baseline characteristics of study participants

Variable	NFG (n = 4,113,399)	IFG (n = 1,402,179)	Early DM (n = 431,634)	Late DM (n = 252,417)	No AF (n = 6,072,361)	Incident AF (n = 127,268)
Age (year)	45.3 ± 14.3	50.5 ± 13.6	56.0 ± 12.2	61.8 ± 9.9	47.6 ± 14.4	61.1 ± 12.9
Age ≥65 years	470,250 (11.4%)	238,816 (17.0%)	113,199 (26.2%)	106,035 (42.0%)	870,152 (14.3%)	58,148 (45.7%)
Male	2,204,748 (53.6%)	882,712 (63.0%)	272,509 (63.1%)	137,369 (54.4%)	3,424,157 (56.4%)	73,181 (57.5%)
Body mass index (kg/m^2)	23.5 ± 3.2	24.5 ± 3.2	25.3 ± 3.3	24.7 ± 3.1	23.8 ± 3.2	24.5 ± 3.3
Body mass index ≥25 (kg/m^2)	1,194,465 (29.0%)	577,678 (41.2%)	219,944 (51.0%)	107,605 (42.6%)	2,046,552 (33.7%)	53,140 (41.8%)
Waist circumference (cm)	79.2 ± 8.9	82.8 ± 8.5	85.8 ± 8.4	85.3 ± 8.2	80.7 ± 9.0	84.2 ± 8.8
Current smoking	1,078,154 (26.2%)	385,097 (27.5%)	119,947 (27.8%)	49,410 (19.6%)	1,606,322 (26.5%)	26,286 (20.7%)
Low income (Lowest 20 percentile)	809,717 (19.7%)	267,586 (19.1%)	94,917 (22.0%)	55,283 (21.9%)	1,201,155 (19.8%)	26,438 (20.7%)
Drinking ≥ 30 g of alcohol per day	247,952 (6.0%)	126,918 (9.1%)	41,067 (9.5%)	15,106 (6.0%)	421,706 (6.9%)	9,337 (7.3%)
Regular exercise	2,125,152 (51.7%)	730,865 (52.1%)	214,930 (49.8%)	121,175 (48.0%)	3,134,640 (51.6%)	57,482 (45.2%)
Hypertension	935,505 (22.7%)	539,017 (38.4%)	246,496 (57.1%)	166,189 (65.8%)	1,813,727 (29.9%)	73,480 (57.7%)
Dyslipidemia	627,549 (15.3%)	342,144 (24.4%)	175,220 (40.6%)	116,679 (46.2%)	1,224,809 (20.2%)	36,783 (28.9%)
Chronic kidney disease	231,868 (5.6%)	107,428 (7.7%)	42,557 (9.9%)	42,535 (16.9%)	407,039 (6.7%)	17,349 (13.6%)
Peripheral artery disease	166,714 (4.1%)	86,798 (6.2%)	51,933 (12.0%)	48,707 (19.3%)	337,766 (5.6%)	16,386 (12.9%)
Fasting glucose level (mg/dL)	87.7 ± 7.6	107.9 ± 6.6	142.8 ± 42.3	147.6 ± 51.2	98.4 ± 24.6	104.6 ± 29.7
Cholesterol (mg/dL)	192.6 ± 35.3	201.7 ± 37.3	199.6 ± 41.3	188.9 ± 40.2	195.0 ± 36.6	194.8 ± 37.9
Systolic blood pressure (mm Hg)	121.0 ± 14.6	126.5 ± 15.0	129.4 ± 15.6	129.1 ± 15.8	123.1 ± 15.1	128.7 ± 16.2
Diastolic blood pressure (mm Hg)	75.7 ± 9.7	78.7 ± 9.9	79.7 ± 10.1	77.7 ± 9.9	76.7 ± 9.9	78.8 ± 10.2
GFR (mL/min/1.73m^2)	88.6 ± 56.7	84.4 ± 35.0	84.7 ± 37.2	80.9 ± 33.8	87.2 ± 50.8	81.8 ± 40.0

The data are presented as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. NFG was defined as those with <100 mg/dL of fasting blood glucose at index health examination and no previous history of type 2 diabetes; IFG was defined as those with ≥100 mg/dL and <126 mg/dL of fasting blood glucose at index health examination and no previous history of type 2 diabetes; Early DM was defined as subjects who diagnosed as type 2 diabetes less than 5 years from index health examination; Late DM was defined as subjects who diagnosed as type 2 diabetes over 5 years from index health examination. Dyslipidemia was defined as total cholesterol ≥240 mg/dL or ICD-10-CM diagnostic code (E78). AF = atrial fibrillation; DM = diabetes mellitus; GFR = glomerular filtration rate; IFG = impaired fasting glucose; NFG = normal fasting glucose.

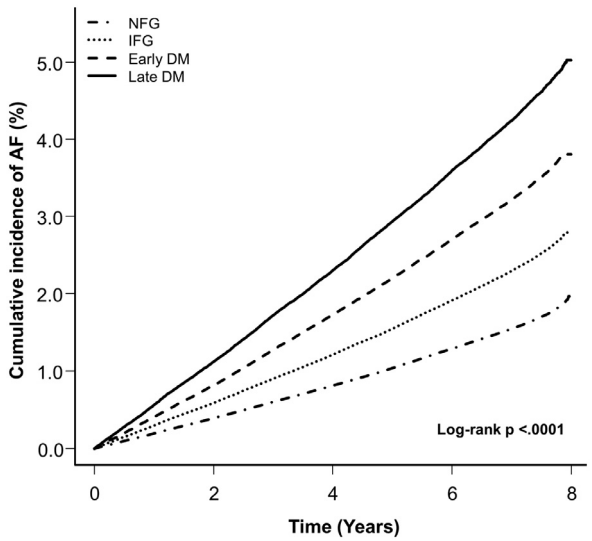

Figure 1. Cumulative incidence of atrial fibrillation according to the time course of type 2 diabetes. (1) NFG was defined as those with <100 mg/dL of fasting blood glucose at index health examination and no previous history of type 2 diabetes; (2) IFG was defined as those with ≥100 mg/dL and <126 mg/dL of fasting blood glucose at index health examination and no previous history of type 2 diabetes; (3) early DM was defined as subjects who diagnosed as type 2 diabetes less than 5 years from index health examination; and (4) late DM was defined as subjects who diagnosed as type 2 diabetes over 5 years from index health examination. AF = atrial fibrillation; DM = diabetes mellitus; IFG = impaired fasting glucose; NFG = normal fasting glucose.

adjustment, all subgroups showed attenuation of the increasing trend. This attenuation was more prominent in the subgroup with old age (≥65 years), excessive alcohol consumption, hypertension, and dyslipidemia.

The baseline characteristics according to the use of antidiabetics medication is summarized in Supplementary Table 3. The risk of AF adjusted for covariates according to fasting glucose level is shown in Figure 2. In the entire population of 6,199,629 subjects, the risk of AF significantly increased with an increment of fasting blood glucose (p-for-trend <0.0001, Figure 2A). In particular, subjects with ≥160 mg/dL of fasting blood glucose showed a 16% increased risk of incident AF compared with those with 80 to 89 mg/dL of fasting blood glucose (aHR 1.16, 95% 1.12 to 1.19). The positive correlation between fasting blood glucose levels and the risk of AF was consistent in 5,706,124 subjects who did not receive antidiabetic medication (p-for-trend <0.0001, Figure 2B). However, in 493,505 subjects who received antidiabetic medication, there was a U-shaped relationship between fasting blood glucose and the risk of incident AF (Figure 2C). Below 130 mg/dL of fasting blood glucose, the risk of AF tended to increase with a decrement of fasting blood glucose, and it reached the highest in the subjects with <80 mg/dL of fasting blood glucose. Above 140 mg/dL of fasting blood glucose, the risk of AF increased with an increment of the fasting blood glucose. Regarding the type of antidiabetic medication, a U-shaped relationship between fasting blood glucose and the risk of incident AF was prominent in those who received oral hypoglycemics (Supplementary Figure 3).

Table 2
Risk of atrial fibrillation according to the time course of type 2 diabetes

	Event number	Incidence rate per 1000 person-year	HR (95% CI) Model1*	HR (95% CI) Model2†
NFG	67,893	2.28	1 (ref)	1 (ref)
IFG	34,092	3.39	1.10 (1.08-1.11)	1.04 (1.02-1.05)
Early DM	14,407	4.74	1.17 (1.15-1.19)	1.06 (1.04-1.08)
Late DM	10,876	6.27	1.19 (1.16-1.21)	1.09 (1.07-1.11)

* Adjusted for age, sex.
† Adjusted for age, sex, body mass index, current smoking, drinking ≥30 g alcohol per day, lower income (lowest 20 percentile), regular exercise, the presence of hypertension, and dyslipidemia. The definition of NFG, IFG, early DM, and late DM was as in Table 1. CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glucose; NFG = normal fasting glucose.

Discussion

To the best of our knowledge, this is the largest study reporting the relationship of the time course of type 2 diabetes with the risk of AF in a general population-based study. The main findings of our study are as follows: (1) the risk of AF sequentially increased across the subjects with NFG, IFG, early DM, and late DM; (2) the risk of AF was significantly higher in subjects who developed type 2 diabetes in the IFG group; (3) fasting blood glucose correlated with the risk of AF in subjects who did not receive antidiabetic medication, whereas there was a U-shaped relationship between fasting glucose level and the risk of AF in those receiving antidiabetic medication.

The association of IFG with an increased risk of AF has previously been reported,[5,9] and there was a case-controlled study on a small cohort reported the association of the duration of type 2 diabetes and the risk of AF.[7] However, the direct comparison of the risk of AF among NFG, IFG, early DM, and late DM has never been studied. In the current study, an increased risk of AF was observed across NFG, IFG, early DM, and late DM. Among those with IFG, subjects who developed type 2 diabetes showed an increased risk of AF than those who did not, which suggests that the risk of AF correlated with the time course of type 2 diabetes. Long-term duration of type 2 diabetes is closely associated with microvascular complication of type 2 diabetes.[10] Accordingly, our findings might be reflective of the association between vascular complication of type 2 diabetes related to long-term duration and AF development given that those with a microvascular complication of type 2 diabetes were at significantly higher risk of AF development in the recent study.[6] Therefore, patients with type 2 diabetes, starting from the prediabetes stage, were required to be regularly screened for AF along with IFG/type 2 diabetes progression.

Although the pathophysiological mechanism of the association between AF and IFG/type 2 diabetes development is controversial, the effect of accompanying risk factors such as hypertension, obesity, and metabolic dysfunction on the risk of AF development needed to be considered.[11] Particularly, the proportion of subjects with obesity increased with the time course of diabetes in this study. Obesity and AF were highly interrelated even in subjects with metabolically healthy.[12,13] Furthermore, cardiac structural changes induced by obesity could play a role in the pathogenesis of AF.[14] In addition, the increasing trend toward the time course of type 2 diabetes was further attenuated by old age, excessive alcohol consumption, the presence of hypertension and dyslipidemia in the present study. In this regard, various risk factors for AF development such as age, metabolic risk factor, co-morbidities should be considered altogether in risk stratification of AF development in patients with prediabetes and type 2 diabetes.

The increasing trend of risk for AF development with an increment of fasting blood glucose was previously reported.[9,15] However, previous studies mainly focused on the range near the cut-off of IFG or type 2 diabetes. We divided the population into 10 groups in a wide range of fasting blood glucose and confirmed that the risk of AF generally correlated with fasting blood glucose levels. To the best of our knowledge, this is the first detailed study describing the risk of AF in relation to fasting blood glucose levels. Fasting blood glucose could be a surrogate marker in the prediction of future AF development, particularly for the subgroup that did not receive antidiabetic mediation. In contrast, strict control of fasting blood glucose in patients who already received antidiabetic medication may have an adverse effect on the AF development according to this study. Severe hypoglycemia and an increased risk of AF have been reported in a previous study.[16] In other studies, oral hypoglycemic medication or insulin inducing frequent hypoglycemia might increase the risk of AF.[17,18] Although fasting blood glucose at a single point is not representative of the overall status of glycemic control, our findings suggest that clinicians should be aware of the possibility of an increased risk of AF in strict control of hyperglycemia.

This study has several limitations. Firstly, the definitions of covariates and endpoints and the assessment of the duration of type 2 diabetes were mainly based on claims data, which might cause misclassification or selection bias. However, this methodology has been used and validated in many studies[6,19,20] and has therefore been adopted for this research. Secondly, although we defined the onset of diabetes as the date of diagnosis listed on the claims database, the exact time course of diabetes would be longer considering subclinical diabetes. Thirdly, the extrapolation of our findings to other ethnicities would be limited because this study was performed among Koreans. Therefore, further investigations regarding the association of the time course of diabetes with AF development in other ethnicities would be needed.

In conclusion, the risk of AF increased with the time course of type 2 diabetes from the prediabetic stage to long duration of type 2 diabetes. Fasting blood glucose correlated with the risk of AF in subjects who did not receive

Table 3
Association of the time course of type 2 diabetes with incident atrial fibrillation in subgroups

	Event number	Incidence rate per 1000 person-year	HR (95% CI) Unadjusted	p for interaction	HR (95% CI) Model1*	p for interaction	HR (95% CI) Model2†	p for interaction
Male				<.0001		0.030		0.097
NFG	36969	2.32	1 (ref)		1 (ref)		1 (ref)	
IFG	21065	3.34	1.44 (1.42-1.46)		1.10 (1.08-1.12)		1.05 (1.03-1.07)	
Early DM	9050	4.75	2.05 (2.00-2.10)		1.20 (1.17-1.22)		1.09 (1.06-1.11)	
Late DM	6097	6.56	2.84 (2.76-2.92)		1.18 (1.15-1.22)		1.09 (1.06-1.12)	
Female								
NFG	30924	2.23	1(ref.)		1(ref.)		1(ref.)	
IFG	13027	3.48	1.56 (1.53-1.59)		1.09 (1.06-1.11)		1.02 (1.00-1.05)	
Early DM	5357	4.73	2.12 (2.06-2.18)		1.12 (1.09-1.16)		1.01 (0.98-1.04)	
Late DM	4779	5.94	2.67 (2.59-2.75)		1.19 (1.15-1.23)		1.09 (1.06-1.13)	
Age <65 years				<.0001		<.0001		<.0001
NFG	38918	1.46	1 (ref)		1 (ref)		1 (ref)	
IFG	18677	2.21	1.51 (1.49-1.54)		1.14 (1.12-1.16)		1.06 (1.05-1.08)	
Early DM	7197	3.15	2.16 (2.10-2.21)		1.26 (1.23-1.29)		1.11 (1.08-1.14)	
Late DM	4328	4.17	2.85 (2.76-2.94)		1.34 (1.30-1.39)		1.21 (1.17-1.25)	
Age ≥65 years								
NFG	28975	9.01	1(ref.)		1(ref.)		1(ref.)	
IFG	15415	9.49	1.06 (1.03-1.08)		1.04 (1.02-1.06)		1.00 (0.98-1.02)	
Early DM	7210	9.56	1.06 (1.04-1.09)		1.06 (1.03-1.08)		1.00 (0.97-1.02)	
Late DM	6548	9.43	1.05 (1.02-1.08)		1.06 (1.03-1.08)		1.01 (0.98-1.04)	
Current smoker				<.0001		<.0001		<.0001
NFG	13850	1.78	1(ref.)		1(ref.)		1(ref.)	
IFG	7250	2.63	1.48 (1.44-1.53)		1.15 (1.12-1.19)		1.09 (1.06-1.12)	
Early DM	3289	3.92	2.21 (2.13-2.30)		1.26 (1.21-1.31)		1.13 (1.09-1.18)	
Late DM	1897	5.66	3.21 (3.06-3.36)		1.27 (1.21-1.33)		1.16 (1.10-1.22)	
Non-current smoker								
NFG	54043	2.46	1(ref.)		1(ref.)		1(ref.)	
IFG	26842	3.68	1.50 (1.48-1.52)		1.08 (1.07-1.10)		1.02 (1.01-1.04)	
Early DM	11118	5.06	2.06 (2.02-2.10)		1.14 (1.12-1.17)		1.03 (1.01-1.06)	
Late DM	8979	6.42	2.62 (2.56-2.68)		1.17 (1.14-1.19)		1.08 (1.05-1.10)	
Drinking ≥30 g alcohol per day				0.617		0.383		0.306
NFG	4215	2.27	1(ref.)		1(ref.)		1(ref.)	
IFG	3086	3.39	1.45 (1.38-1.51)		1.09 (1.04-1.15)		1.05 (1.00-1.10)	
Early DM	1388	4.73	2.05 (1.93-2.18)		1.22 (1.15-1.30)		1.12 (1.05-1.19)	
Late DM	648	6.27	2.68 (2.46-2.91)		1.16 (1.07-1.27)		1.08 (0.99-1.17)	
Drinking <30 g alcohol per day								
NFG	63678	2.35	1(ref.)		1(ref.)		1(ref.)	
IFG	31006	3.40	1.49 (1.47-1.51)		1.09 (1.08-1.11)		1.04 (1.02-1.05)	
Early DM	13019	4.82	2.08 (2.04-2.12)		1.16 (1.13-1.19)		1.05 (1.03-1.07)	
Late DM	10228	6.27	2.77 (2.71-2.83)		1.19 (1.16-1.21)		1.09 (1.08-1.12)	

(*continued on next page*)

Table 3 (*Continued*)

	Event number	Incidence rate per 1000 person-year	HR (95% CI) Unadjusted	p for interaction	HR (95% CI) Model1*	p for interaction	HR (95% CI) Model2†	p for interaction
Lower income (lowest 20 percentile)				0.014		0.057		0.072
NFG	13981	2.39	1(ref.)		1(ref.)		1(ref.)	
IFG	6789	3.55	1.49 (1.45-1.53)		1.07 (1.04-1.10)		1.01 (0.98-1.04)	
Early DM	3242	4.88	2.05 (1.97-2.13)		1.18 (1.13-1.22)		1.06 (1.02-1.10)	
Late DM	2336	6.16	2.59 (2.48-2.71)		1.21 (1.16-1.27)		1.11 (1.06-1.16)	
Middle or upper income (Upper 80 percentile)								
NFG	53912	2.25	1(ref.)		1(ref.)		1(ref.)	
IFG	27303	3.35	1.49 (1.47-1.51)		1.10 (1.09-1.12)		1.04 (1.03-1.06)	
Early DM	11165	4.70	2.09 (2.05-2.13)		1.17 (1.14-1.19)		1.05 (1.03-1.08)	
Late DM	8540	6.31	2.81 (2.74-2.87)		1.18 (1.15-1.21)		1.09 (1.06-1.11)	
Dyslipidemia								
NFG	15972	3.53	1(ref.)	<.0001	1(ref.)	<.0001	1(ref.)	<.0001
IFG	10152	4.14	1.17 (1.14-1.20)		1.06 (1.03-1.08)		1.01 (0.99-1.04)	
Early DM	5764	4.64	1.31 (1.28-1.36)		1.08 (1.05-1.12)		1.00 (0.97-1.03)	
Late DM	4895	6.06	1.72 (1.66-1.77)		1.16 (1.12-1.20)		1.10 (1.06-1.13)	
Without dyslipidemia								
NFG	51921	2.05	1(ref.)		1(ref.)		1(ref.)	
IFG	23940	3.15	1.53 (1.51-1.56)		1.10 (1.09-1.12)		1.05 (1.03-1.06)	
Early DM	8643	4.81	2.34 (2.29-2.40)		1.20 (1.18-1.23)		1.09 (1.06-1.11)	
Late DM	5981	6.46	3.15 (3.07-3.24)		1.18 (1.15-1.21)		1.08 (1.05-1.11)	
Hypertension								
NFG	34230	5.15	1(ref.)	<.0001	1(ref.)	<.0001	1(ref.)	<.0001
IFG	20668	5.42	1.05 (1.04-1.07)		1.01 (0.99-1.02)		0.99 (0.97-1.01)	
Early DM	10319	6.00	1.17 (1.14-1.19)		1.04 (1.02-1.06)		1.01 (0.99-1.03)	
Late DM	8263	7.32	1.43 (1.39-1.46)		1.07 (1.04-1.10)		1.06 (1.03-1.08)	
Without hypertension								
NFG	33663	1.45	1(ref.)		1(ref.)		1(ref.)	
IFG	13424	2.15	1.48 (1.45-1.51)		1.12 (1.10-1.14)		1.10 (1.07-1.12)	
Early DM	4088	3.10	2.13 (2.07-2.20)		1.18 (1.14-1.22)		1.14 (1.10-1.18)	
Late DM	2613	4.32	2.98 (2.86-3.10)		1.18 (1.13-1.23)		1.16 (1.18-1.21)	

* Adjusted for age, sex.

† Adjusted for age, sex, current smoking, body mass index, drinking ≥30 g alcohol per day, lower income (lowest 20 percentile), regular exercise, the presence of hypertension, and dyslipidemia. The definition of NFG, IFG, early DM, and late DM was as in Table 1. CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired glucose tolerance; NFG = normal fasting glucose.

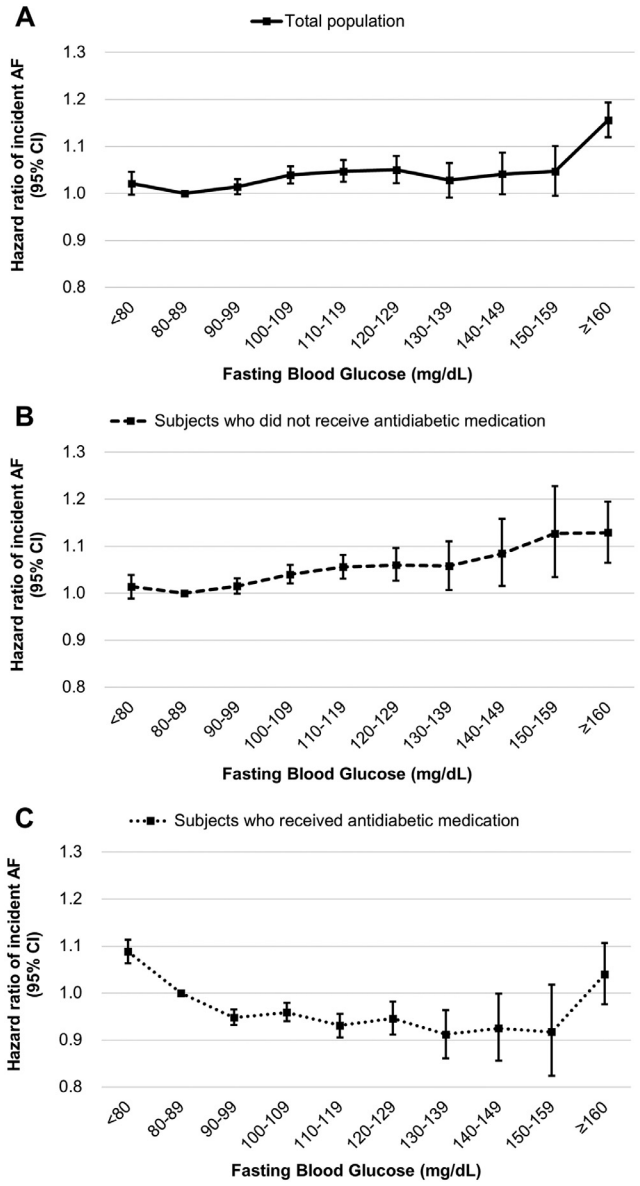

Figure 2. Risk of atrial fibrillation according to fasting blood glucose in (*A*) total population, (*B*) subjects who did not receive antidiabetic medication, and (*C*) subjects who received antidiabetic medication. AF = atrial fibrillation; CI = confidence interval.

antidiabetic medication. However, low blood glucose level was associated with an increased risk of AF in subjects who received antidiabetic medication. Therefore, clinicians should consider starting AF surveillance in patients with prediabetes and should give more attention to the patients with long duration of type 2 diabetes in the prediction of AF. In the therapeutic aspect, clinicians should be cautious of an increased risk of AF if blood glucose is controlled strictly by using antidiabetic medication.

Authors Contributions

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Supplementary materials

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