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Association Between Atrial Fibrillation and Diabetes-Related Complications: A Nationwide Cohort Study

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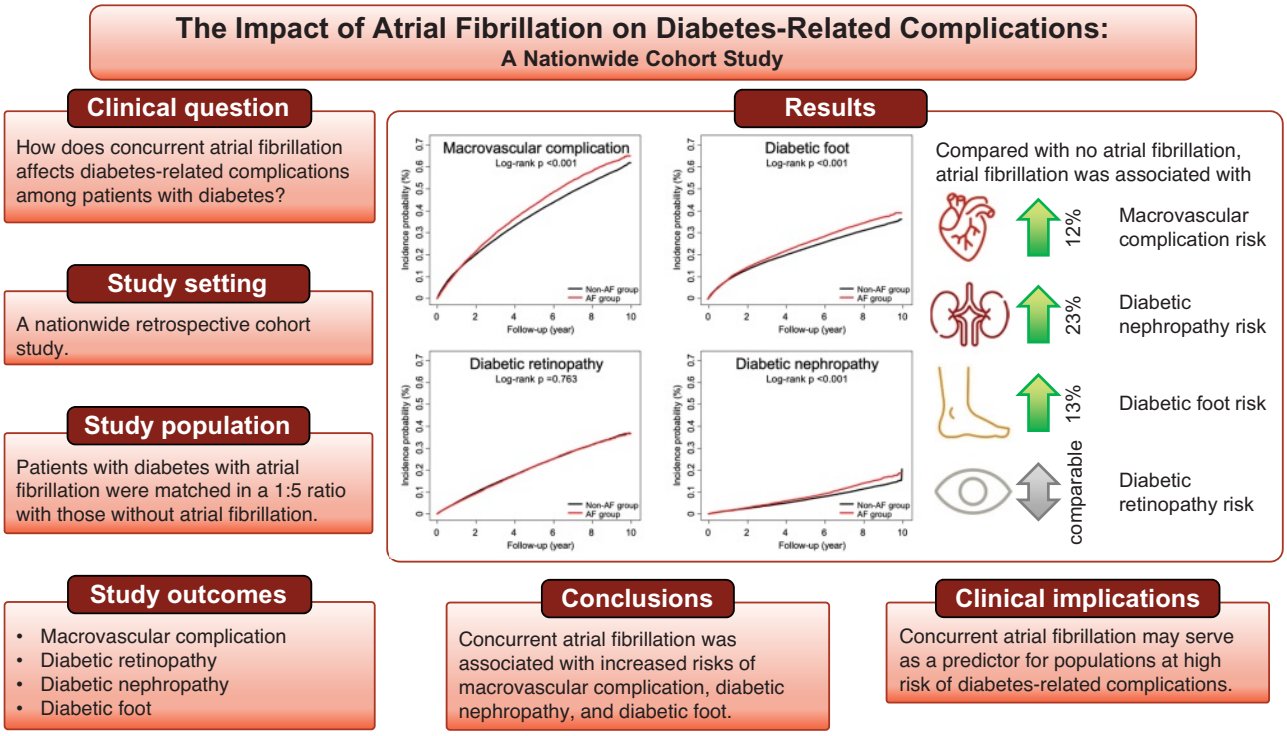

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Atrial fibrillation is prevalent in patients with diabetes, yet the impact of atrial fibrillation on diabetes-related complications is not well known.
- **What is the specific question we wanted to answer?**
  This study aimed to investigate the impact of concurrent atrial fibrillation on diabetes-related complications.
- **What did we find?**
  The study found that concurrent atrial fibrillation was associated with increased risks of macrovascular complications, diabetic nephropathy, and diabetic foot complications. Specifically, patients with diabetes and concurrent atrial fibrillation had a significantly higher risk of diabetic foot amputation.
- **What are the implications of our findings?**
  These findings suggest that concurrent atrial fibrillation may serve as a predictor for populations at a high risk of diabetes-related complications.

Association Between Atrial Fibrillation and Diabetes-Related Complications: A Nationwide Cohort Study

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OBJECTIVE

This study aimed to investigate the associations between concurrent atrial fibrillation and diabetes-related complications among patients with diabetes.

RESEARCH DESIGN AND METHODS

This nationwide observational cohort study used the health checkup database from the Korean National Health Insurance Service. Patients diagnosed with diabetes who underwent health checkups between 2009 and 2012 were investigated. The patients with atrial fibrillation were matched in a 1:5 ratio with those without atrial fibrillation using propensity scores. Study outcomes included macrovascular, microvascular (diabetic retinopathy and diabetic nephropathy), and diabetic foot complications. The risks of clinical outcomes were measured using hazard ratios (HRs) with 95% CIs.

RESULTS

A total of 65,760 patients with diabetes were analyzed (54,800 without atrial fibrillation and 10,960 with atrial fibrillation). After well-balanced propensity score matching, atrial fibrillation was associated with significantly higher risks of macrovascular complications (HR 1.12, 95% CI 1.09–1.16), diabetic nephropathy (HR 1.23, 95% CI 1.16–1.30), and diabetic foot complications (HR 1.13, 95% CI 1.09–1.17) compared with no atrial fibrillation, while the risk of diabetic retinopathy was comparable (HR 0.99, 95% CI 0.96–1.03). Patients with atrial fibrillation had a significantly higher risk of diabetic foot amputation (HR 4.12, 95% CI 1.98–8.56).

CONCLUSIONS

Among patients with diabetes, concurrent atrial fibrillation was associated with increased risks for diabetes-related macrovascular complications, diabetic nephropathy, and diabetic foot. Such patients require holistic management to reduce the risk of adverse outcomes.

Diabetes is a global health concern, with the number of adults affected increasing annually (1). According to the International Diabetes Federation, ∼537 million adults had diabetes in 2021, and this number is expected to rise to 783 million by 2045 (1). As a result, the incidence of diabetes-related complications has been increasing in recent years (2–4). Poorly managed diabetes can result in chronic complications, which not only worsen the prognosis for patients with diabetes but also increase health care

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costs (5). Therefore, identifying high-risk populations is crucial for managing diabetes and reducing complications.

Atrial fibrillation (AF) is the most common arrhythmia, and its worldwide prevalence has increased by 33% over the past 20 years (6). When diabetes is present, there is an increased risk of developing AF by 35–60% (7,8). Diabetes and AF are linked with an increased risk of morbidity and mortality, and the coexistence of these two conditions can lead to worse patient outcomes. For example, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study found that among patients with diabetes, concurrent AF increased cardiovascular mortality and heart failure by 77% and 68%, respectively (9). Therefore, concurrent AF may predict poor prognosis in patients with diabetes.

Despite the potential link between AF and diabetes-related complications, few studies have investigated this association, and evidence remains limited for diabetic retinopathy and diabetic foot complications (10,11). Given the rising prevalence of AF among people with diabetes, it is crucial to understand the impact of AF on the risks of various types of diabetes-related complications. Therefore, this study aimed to investigate the associations between the coexistence of AF and diabetes-related macrovascular and microvascular complications in a nationwide population cohort with diabetes.

RESEARCH DESIGN AND METHODS

Data Source

This study retrospectively used a nationwide cohort of patients with diabetes who underwent health checkups between 2009 and 2012 provided by the National Health Insurance Service (NHIS) of South Korea. The NHIS database comprises individual results of health checkups and claims with diagnostic, procedural, and prescription codes (12). Because the NHIS is the sole public insurer in South Korea, its database represents the Korean population. The health checkup database comprises demographic information, including body measurements, blood and urine tests, and survey results on health habits. This study adhered to the Declaration of Helsinki, revised in 2013, and was approved by the institutional review board of Seoul National University Hospital (no. 2211-067-1377). Informed consent was exempted because the study only used retrospective, deidentified data.

Study Population

The presence of diabetes was defined as having a diagnostic code for diabetes (E11–E14 according to the ICD-10-CM) and a prescription for an antihyperglycemic drug (sulfonylurea, metformin, meglitinide, thiazolidinedione, dipeptidyl peptidase 4 [DPP-4] inhibitor, α-glucosidase inhibitor, or insulin) during either inpatient admission (one or more) or outpatient (two or more) visits. There were 2,746,078 individuals with diabetes in the initial population who underwent health checkups between 2009 and 2012. Among health checkups, the earliest checkup was defined as the index checkup. Individuals who had macrovascular complications (myocardial infarction, ischemic stroke, and peripheral artery disease), microvascular complications (diabetic retinopathy and nephropathy), diabetic foot, or neuropathies within 1 year before the index checkup were excluded (n = 509,908, 164,423, 193,616, and 79,202, respectively). Additionally, individuals aged <30 years or those with missing values for study covariates were excluded. We excluded patients aged <30 years because most AF cases occur after the age of 30 (13). The remaining population was divided into non-AF (n = 1,630,475) and AF (n = 15,693) groups. The AF group was defined as individuals with diagnostic codes I48.0–I48.4 or I48.9 for at least one admission or two outpatient visits 3 years before the index checkup. The two groups were matched 1:5 using propensity scores (PSs). Consequently, the study included 54,800 and 10,960 patients in the non-AF and AF groups, respectively (Supplementary Fig. 1).

Study Covariates

All study covariates were obtained from the NHIS database during the index health checkup. The covariates included age, sex, smoking status (categorized as never smoker, ex-smoker, or current smoker), alcohol consumption (classified as a nondrinker, mild drinker, or heavy drinker based on alcohol consumption of 0 g/day, <30 g/day, or ≥30 g/day, respectively), regular exercise (indicated if a patient performed moderate physical activity for >30 min in ≥5 days/week or strenuous physical activity for >20 min in ≥3 days/week), low-income status (indicated if a patient's annual income was in the lower 10th percentile of the income distribution of the entire Korean population), and diabetes duration (<5 years or ≥5 years). We also examined a list of comorbidities, which included hypertension, dyslipidemia, ischemic heart disease, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and cancer. Information on individual comorbidities was identified from disease codes available in the NHIS database. In addition, we examined concomitant drug use, which included oral hypoglycemic agents (OHAs) (sulfonylureas, meglitinides, metformin, thiazolidinediones, α-glucosidase inhibitor, and DPP-4 inhibitors), insulin, antihypertensive drugs (β-blockers, calcium channel blockers, ACE inhibitors, aldosterone receptor blockers, and diuretics), statins, antiplatelet agents, and oral anticoagulants. We also examined health checkup data, including body mass index (BMI), systolic and diastolic blood pressures, fasting blood glucose, total cholesterol, HDL and LDL cholesterols, estimated glomerular filtration rate (eGFR), and triglycerides. A complete list for the definitions of the study covariates are summarized in Supplementary Table 1.

Study Outcomes

The study outcomes were macrovascular complications, diabetic retinopathy, diabetic nephropathy, and diabetic foot. Macrovascular complications comprised myocardial infarction, stroke, or peripheral artery disease. Among microvascular complications, diabetic retinopathy was further categorized into proliferative and nonproliferative diabetic retinopathy (14). Diabetic nephropathy was defined as the presence of diabetes with any of the following four conditions: *1*) diagnostic code during admission or outpatient visits (N18, N19, Z49, Z905, Z94, and Z992), *2*) procedural code for renal transplant (R3280), *3*) procedural code for hemodialysis (O7011–O7020), and *4*) procedural code for peritoneal dialysis (O7071–O7075). Diabetic foot was further categorized into with and without amputation. To define the study outcomes, we used operational definitions based on disease codes and procedural codes available from the NHIS database. The study also investigated all-cause mortality. Detailed definitions of the study outcomes are summarized in Supplementary Table 1. Individuals were followed from their index health checkup

until the occurrence of the study outcome or the end of the follow-up period (31 December 2018). Each study outcome was evaluated independently from one another.

Matching and Statistical Analyses

This study used PS matching to compare the non-AF and AF groups. PSs were determined by calculating the predicted probabilities of belonging to either the non-AF or AF group, using a logistic regression model that incorporated the following covariates: age, sex, smoking, alcohol consumption, regular exercise, low-income status, diabetes duration ($<$5 years or $\geq$5 years), hypertension, dyslipidemia, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, cancer, any OHA, insulin, antihypertensive drugs, oral anticoagulants, antiplatelet agents, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, HDL and LDL cholesterols, eGFR, and triglycerides. Each patient in the AF group was matched to five patients in the non-AF group to enhance the robustness of the statistical analyses. We used the nearest neighbor matching method as the matching algorithm, ensuring that matched pairs had a PS caliper of $<$0.01 (15,16). Covariate balance was assessed using the absolute standardized difference (ASD) for each covariate, with values of $<$0.1 considered indicative of balance.

Covariate data are presented as *n* (%), mean ± SD, or median (interquartile range [IQR]), depending on the types of covariates. We compared covariates between the non-AF and AF groups using appropriate statistical tests, such as the *t* test or Mann-Whitney *U* test. The study outcome's incidence rate (IR) was calculated as events per 1,000 person-years. Kaplan-Meier survival analysis was used to analyze event-free survival for the study outcomes, and the log-rank test was used to compare event-free survivals between the two groups. The risks of the study outcomes for the AF group were calculated as hazard ratios (HRs) with 95% CIs, where the non-AF group served as a reference. All statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC). A two-sided $P < 0.05$ was used to reject the null hypothesis.

Subgroup, Sensitivity, and Falsification Analyses

We performed subgroup analyses for age strata ($<$65 years vs. $\geq$65 years), sex, insulin use, OHA use ($<$3 types vs. $\geq$3 types), smoking status (never, ex-, and current smoker), diabetes duration ($<$5 years vs. $\geq$5 years), chronic kidney disease status (yes vs. no), and heart failure status (yes vs. no) to examine the effects of these factors on the study outcomes. Also, three sensitivity analyses were performed to address potential biases. First, given that AF might require a certain duration to influence the onset of diabetes-related complications, we conducted a sensitivity analysis incorporating a 1-year lag period. Second, as the estimation of the probability of the study outcomes can be biased because of mortality, we performed a competing risk analysis that accounted for mortality as a competing event. Third, we conducted a multivariable Cox proportional hazards regression analysis using different sets of covariates for the non-PS–matched population after excluding the patients with insulin use at the baseline, as the PS matching process has the potential to exclude a substantial portion of patients with diabetes and introduce selection bias. Finally, we conducted a falsification analysis for multiple falsification outcomes to ensure that both groups were well balanced. The absence of significant associations between the two groups for the falsification outcomes may indicate that the results can be unbiased. A complete list of falsification outcomes is provided in Supplementary Table 2.

Exploratory Analyses

To assess the impact of selected cardiovascular risk factors (age, fasting blood glucose, BMI, and systolic blood pressure) on the study outcome and to make comparisons between the study groups, we examined cubic spline curves for HRs of the study outcomes in both the non-AF and AF groups.

Data and Resource Availability

The raw data are available to researchers on relevant request and with an approval by the Korean National Health Insurance Sharing Service.

RESULTS

Baseline Characteristics

The study population consisted of 54,800 patients without AF and 10,960 with AF after PS matching. Baseline characteristics before PS matching are provided in Supplementary Table 3. After PS matching, the distribution of PSs of the two groups was well overlapped (Supplementary Fig. 2). Also, the study covariates were well balanced between the two groups (all ASDs $<$0.1) (Table 1). After PS matching, the mean age of the study population was 64.2 ± 11.1 years, and 63.2% were male. Before the matching, the proportion of patients with a diabetes duration $\geq$5 years was higher in the AF group than the non-AF group (28.6% vs. 19.9%, respectively), with an ASD of 0.205 (Supplementary Table 3). However, this imbalance was effectively reduced after the matching, with 27.3% in the AF group and 30.7% in the non-AF group (ASD = 0.075) (Table 1). The most common comorbidities were hypertension (73.2% vs. 71.2%), dyslipidemia (44.5% vs. 43.7%), chronic kidney disease (19.3% vs. 18.7%), and heart failure (13.7% vs. 15.8%) in the non-AF and AF groups, respectively. Metformin (51.2% vs. 48.5%) and sulfonylurea (44.0% vs. 39.9%) were the two most used OHAs in the non-AF and AF groups, respectively.

Risks of Diabetes-Related Complications

All study outcomes, except for diabetic retinopathy, showed significant differences in survival between the two groups, with log-rank $P < 0.001$ (Fig. 1). During the median follow-up period of 7.6 years (IQR 6.1–8.8 years), the AF group had both a significantly higher IR and risk of macrovascular complications (110.7 vs. 98.2 per 1,000 person-years, HR 1.12, 95% CI 1.09–1.16), diabetic nephropathy (18.1 vs. 14.8 per 1,000 person-years, HR 1.23, 95% CI 1.16–1.30), and diabetic foot (54.2 vs. 47.9 per 1,000 person-years, HR 1.13, 95% CI 1.09–1.17) (all $P < 0.001$) compared with the non-AF group (Fig. 2). Among diabetic foot events, the risk of diabetic foot with amputation was significantly higher in the AF group by 4.1-fold (HR 4.12, 95% CI 1.98–8.56) (Fig. 2). There was no significant difference in the risk of diabetic retinopathy between the two groups, with an HR of 0.99 (95% CI 0.96–1.03), even when subcategorized into proliferative and nonproliferative retinopathies (Supplementary Table 4). Regarding all-cause mortality, there was a significant difference in survival curves between study groups (log-rank $P < 0.001$) (Supplementary Fig. 3). The AF group was associated with an increased risk of all-cause mortality compared with the non-AF group (HR 1.36, 95% CI 1.30–1.42) (Supplementary Table 5).

Table 1—Baseline characteristics of the study population after matching

Characteristic	Non-AF group (*n* = 54,800)	AF group (*n* = 10,960)	ASD
Age, years	64.3 ± 11.1	63.8 ± 11.0	0.045
Male sex	34,617 (63.2)	6,942 (63.3)	0.004
Smoking status			
Never smoker	31,824 (58.1)	6,268 (57.2)	0.018
Ex-smoker	13,019 (23.8)	2,548 (23.3)	0.012
Current smoker	9,957 (18.2)	2,144 (19.6)	0.036
Alcohol consumption			
Nondrinker	33,803 (61.7)	6,672 (60.9)	0.016
Mild drinker	15,756 (28.8)	3,190 (29.1)	0.008
Heavy drinker	5,241 (9.6)	1,098 (10.0)	0.016
Regular exercise	11,306 (20.6)	2,202 (20.1)	0.013
Low-income status	12,230 (22.3)	2491 (22.7)	0.010
Diabetes duration ≥5 years	16,882 (30.7)	3,000 (27.3)	0.075
Comorbidity			
Hypertension	40,095 (73.2)	7,806 (71.2)	0.044
Dyslipidemia	24,381 (44.5)	4,786 (43.7)	0.017
Heart failure	7,493 (13.7)	1,732 (15.8)	0.060
Chronic obstructive pulmonary disease	7,749 (14.1)	1,655 (15.1)	0.027
Chronic kidney disease	10,575 (19.3)	2,051 (18.7)	0.015
Cancer	586 (1.1)	168 (1.5)	0.041
Concomitant drug			
Any OHA	35,436 (64.7)	6,793 (62.0)	0.056
Sulfonylurea	24,127 (44.0)	4,370 (39.9)	0.084
Meglitinide	828 (1.5)	162 (1.5)	0.003
Metformin	28,049 (51.2)	5,322 (48.6)	0.052
Thiazolidinedione	3,055 (5.6)	493 (4.5)	0.049
α-Glucosidase inhibitor	5,866 (10.7)	1,169 (10.7)	0.001
DPP-4 inhibitor	4,801 (8.8)	909 (8.3)	0.017
Insulin	4,311 (7.9)	1,170 (10.7)	0.097
Antihypertensive drug	36,946 (67.4)	7,092 (64.7)	0.057
Statin	20,407 (37.2)	3,993 (36.4)	0.017
Oral anticoagulant	538 (1.0)	168 (1.5)	0.049
Antiplatelet agent	33,377 (60.9)	6,700 (61.1)	0.005
Health checkup data			
BMI, kg/m^2	25.3 ± 3.5	25.2 ± 3.5	0.023
Blood pressure, mmHg			
Systolic	128.2 ± 15.4	128.5 ± 16.2	0.017
Diastolic	78.3 ± 10.1	78.6 ± 10.6	0.024
Fasting blood glucose, mg/dL	137.0 ± 40.7	137.5 ± 40.9	0.010
Cholesterol, mg/dL			
Total	183.5 ± 39.8	185.5 ± 40.5	0.052
HDL	51.3 ± 25.4	51.7 ± 26.7	0.015
LDL	101.4 ± 38.3	103.2 ± 37.0	0.048
eGFR, mL/min/1.73 m^2	79.2 ± 29.5	79.8 ± 37.6	0.018
Triglycerides, mg/dL, geometric mean (95% CI)	137.7 (137.1–138.3)	137.4 (136.0–138.9)	0.003

Data are mean ± SD or *n* (%) unless otherwise indicated.

Subgroup Analyses

A significant sex-dependent interaction was observed only for diabetic nephropathy, with females being more vulnerable to diabetic nephropathy in the presence of AF (HR 1.14 [95% CI 1.06–1.23] in males and 1.40 [95% CI 1.27–1.54] in females for the AF group compared with the non-AF group, *P* for interaction = 0.001) (Supplementary Fig. 4). The use of insulin showed a significant interaction for all complications except for diabetic retinopathy (*P* for interaction < 0.001, 0.004, and < 0.001 for macrovascular complications, diabetic nephropathy, and diabetic foot, respectively). Patients who used insulin had an accentuated hazardous effect of AF. While the subgroup of age strata (<65 years vs. ≥65 years) showed a significant interaction for diabetic retinopathy (*P* for interaction = 0.008), no significant difference was observed in the risk of diabetic retinopathy between the non-AF and AF groups. Other subgroups based on the presence of chronic kidney disease, duration of diabetes (<5 years vs. ≥5 years), and number of concomitant OHAs (fewer than three types vs. three or more types) did not show significant interactions for the study outcomes.

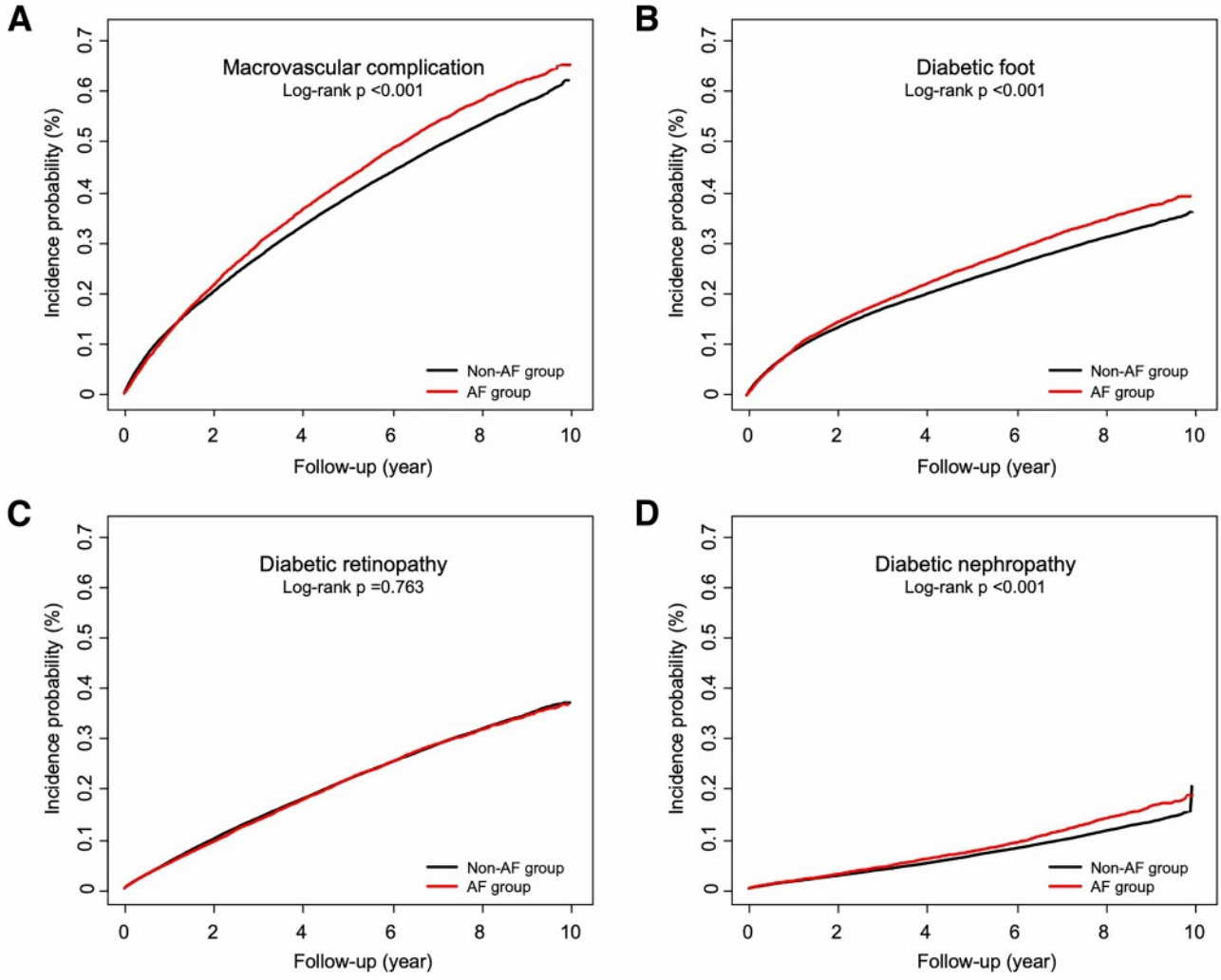

Figure 1—Event curves for diabetes-related chronic complications with and without AF. Compared with the non-AF group, the AF group showed significantly higher incidences of diabetes-related chronic complications except for diabetic retinopathy. *A*: Macrovascular complications. *B*: Diabetic foot complications. *C*: Diabetic retinopathy. *D*: Diabetic nephropathy.

Sensitivity and Falsification Analyses

The results were coherent with the primary findings if we followed the study population from one year after the index health checkup or if we performed a competing risk analysis for the study outcomes (Table 2). Similar results were reproduced when we performed a multivariable Cox proportional hazards regression analysis for the non-PS–matched population (Supplementary Table 6). Additionally, the risk for each falsification outcome was comparable between the two groups (Supplementary Table 7), indicating that the results may be unbiased.

Exploratory Analyses

There were increasing risks of macrovascular complications and diabetic nephropathy with older age, regardless of concurrent AF (Supplementary Fig. 5). As shown in Supplementary Figs. 6–8, we observed a U-shaped response between the fasting blood glucose level and the study outcomes in both the non-AF and AF groups. Additionally, we found that the impact of BMI and blood pressure on study outcomes was not as pronounced as that of fasting blood glucose. These findings may indicate that the influence of selected cardiovascular risk factors on the study outcomes was generally comparable in both groups.

CONCLUSIONS

To our knowledge, this study is the largest to examine the associations between concurrent AF and diabetes-related complications using a population-based nationwide cohort of patients with diabetes. Our findings revealed that patients with diabetes and concurrent AF had a 12% higher risk of macrovascular complications, a 23% higher risk of diabetic nephropathy, and a 13% higher risk of diabetic foot than those without AF. However, there was no significant association between AF and diabetic retinopathy. We also observed that the impact of AF on diabetes-related complications was more accentuated among patients who used insulin than those who did not.

This study has the following strengths. First, it used a population-based cohort, enabling the investigation of a large and representative population of patients with diabetes. Second, the study implemented PS matching to reduce confounding factors between patients with diabetes with and without concurrent AF. By balancing covariates between the two groups, the PS matching can improve the accuracy of estimating the effect of concurrent AF, despite the retrospective study design. Also,

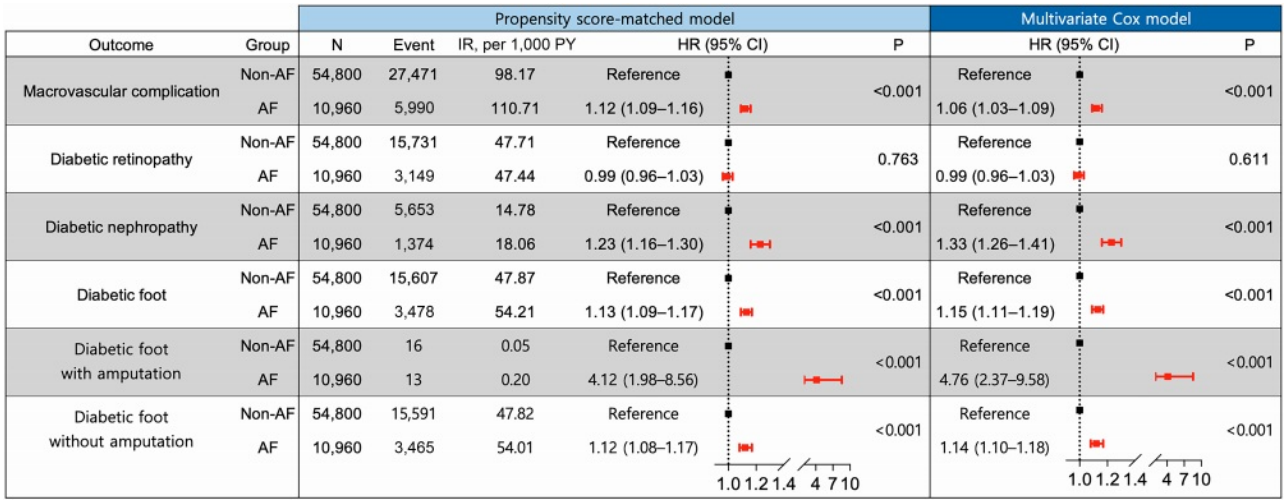

Figure 2—Risks of diabetes-related chronic complications with and without AF. The presence of AF among patients with diabetes increased the risks of diabetes-related chronic complications, except for diabetic retinopathy. The analysis used adjusted for covariates, including age, sex, smoking, alcohol consumption, regular exercise, low-income status, diabetes duration, hypertension, dyslipidemia, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, cancer, OHAs, insulin, antihypertensive drugs, oral anticoagulants, antiplatelet agents, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, HDL and LDL cholesterol, eGFR, and triglycerides. PY, person-year.

our falsification analysis did not suggest major residual confounding, although this cannot be completely excluded.

Advancements in diabetes management and antihyperglycemic medicine have significantly improved the management of diabetes-related complications in recent decades. Previous literature has shown a reduction in the rates of diabetes-related complications between 1990 and 2010, mainly because of a substantial decrease of 67.8% in myocardial infarction (17). However, cardiovascular complications continue to be a significant cause of morbidity and mortality among patients with diabetes. Also, there are limited epidemiological data on other types of diabetes-related complications in the modern era, particularly in developing countries where a higher IR is expected compared with high-income countries (18). Indeed, recent studies have indicated a resurgence of diabetes-related complications after 2010, especially in low- and middle-income countries (2,18). Additionally, the increased prevalence of complications may be due to prolonged exposure to diabetes as patients' life spans have increased (19). This is important since diabetes-related complications have a significant impact not only on patients' prognosis but also on health care costs (20). Thus, identifying high-risk populations for diabetes-related chronic complications is crucial for improving patient management and reducing health care costs.

Concurrent AF has been suggested as a risk factor for adverse outcomes among patients with diabetes (9,11). One randomized controlled trial found that compared with patients with diabetes without AF, those with AF had a 60% increased risk

Table 2—Sensitivity analyses: 1-year lag of follow-up and competing risk analysis

Outcome	Group	*n*	Event	IR, per 1,000 PY	HR (95% CI)	*P*
1-Year lag analysis						
Macrovascular complication	Non-AF	41,252	17,851	87.22	Reference	<0.001
	AF	8,312	4,014	102.72	1.18 (1.14–1.22)	
Diabetic retinopathy	Non-AF	41,252	10,132	43.97	Reference	0.469
	AF	8,312	2,062	44.75	1.02 (0.97–1.07)	
Diabetic nephropathy	Non-AF	41,252	3529	13.58	Reference	<0.001
	AF	8,312	891	17.23	1.27 (1.18–1.37)	
Diabetic foot	Non-AF	41,252	8,855	37.57	Reference	<0.001
	AF	8,312	2,074	45.00	1.20 (1.14–1.25)	
Competing risk analysis						
Macrovascular complication	Non-AF	54,800	27,471	98.17	Reference	<0.001
	AF	10,960	5,990	110.71	1.11 (1.08–1.14)	
Diabetic retinopathy	Non-AF	54,800	15,731	47.71	Reference	0.215
	AF	10,960	3,149	47.44	0.98 (0.94–1.01)	
Diabetic nephropathy	Non-AF	54,800	5,653	14.78	Reference	<0.001
	AF	10,960	1,374	18.06	1.20 (1.13–1.27)	
Diabetic foot	Non-AF	54,800	15,607	47.87	Reference	<0.001
	AF	10,960	3,478	54.21	1.11 (1.07–1.15)	

PY, person-year.

of all-cause mortality and cardiovascular outcomes (9). However, previous literature has focused primarily on cardiovascular and renal outcomes, with little investigation into general diabetes-related complications, such as diabetic retinopathy or diabetic foot (18). Consequently, there is a relative lack of data on whether the development of AF among patients with diabetes increases the risks of these complications. Notably, diabetic retinopathy and diabetic foot critically deteriorate patients' quality of life.

The association between concurrent AF and increased risks of diabetes-related complications may have multifactorial mechanisms. The pathophysiology of AF involves complex interactions among electrical, structural, and genetic factors, resulting in an elevated risk of thromboembolic events and inflammation that may also contribute to the development and progression of diabetes-related complications. Moreover, AF and cardiovascular diseases share common risk factors, such as aging, hypertension, heart failure, obesity, and smoking (21). AF independently contributes to an increased risk of mortality, ischemic heart disease, stroke, chronic kidney disease, and major cardiovascular events, which are subsequently associated with a heightened risk of diabetes-related complications (22). Additionally, increased polypharmacy because of AF may worsen patients' compliance with antihyperglycemic drugs, leading to poor glycemic control and an increased risk of diabetes-related complications.

Concurrent AF and cardiovascular diseases share common risk factors, such as older age, obesity, hypertension, and obstructive sleep apnea (23), which may explain the increased risks of macrovascular complications among patients with concurrent AF. Also, the impact of concurrent AF on macrovascular complications was modest in our study. However, our study primarily focused on assessing the effects of AF alone on diabetes-related complications. By matching most baseline characteristics, including cardiovascular disease, we aimed to minimize confounding effects from these factors and isolate the specific influence of AF on diabetes-related outcomes. In our study, it is possible that underlying cardiovascular diseases influence the observed risk of macrovascular complications, and the impact of AF alone is relatively modest. Regardless of concurrent AF, the underlying atherosclerosis and cardiovascular risk factors of patients with diabetes could have driven the significant impact of diabetes-related complications. Also, some cardiovascular risk factors had similar effects regardless of AF (Supplementary Figs. 5–8). This finding may further explain the modest impact of AF alone on macrovascular complications.

Similarly, AF and chronic kidney disease are interrelated and share risk factors (24), leading to an increased risk of diabetic nephropathy among patients with AF. Besides the shared risk factors, AF itself may exacerbate renal function because of its prothrombotic effect, resulting in renal infarcts, increased systemic inflammation, and activation of the renin-angiotensin-aldosterone system (25). Moreover, medications for AF, such as warfarin, can exacerbate uremic calciphylaxis, further deteriorating renal function. Consequently, patients with diabetes and AF may become more vulnerable to diabetic nephropathy than those without AF.

AF may also worsen diabetic foot by impairing limb blood flow. Indeed, there is evidence that AF is associated with an increased risk of acute limb ischemia (26), and potential mechanisms for developing peripheral artery disease or thromboembolism in the limb arteries have been suggested (27). Additionally, elevated inflammatory markers and endothelial dysfunction accompanied by AF may precipitate the risk of developing peripheral artery disease (28). This, in turn, further increases the risk of diabetic foot complications. Our study demonstrates the association between concurrent AF and increased risks of diabetic foot with and without amputation by 12% and 412%, respectively, suggesting that the risk increases with the severity of diabetic foot. The increased severity of diabetic foot among patients with AF may be attributed to arterial thromboembolism, given that AF is known to be prothrombotic.

Previous literature has shown inconsistent findings regarding the association between the development of AF and an increased risk of retinopathy among patients with diabetes (14,29). However, most studies had relatively small sample sizes compared with ours, which used a larger and more representative population and PS matching to control for confounding factors. Despite these strengths, the underlying mechanisms linking AF and diabetic retinopathy remain poorly understood and warrant further investigation.

Patients with both diabetes and AF represent clinically complex patients at high risk of adverse outcomes, yet evidence-based treatments are often suboptimal (30). Apart from anticoagulation, reducing AF burden or implementing lifestyle modifications in patients with diabetes and concurrent AF may contribute to a decrease in macrovascular complications, such as stroke, subsequently reducing cardiovascular events (31). Therefore, contemporary management of AF, which encompasses anticoagulation, early rhythm control, and lifestyle modification, in a holistic or integrated care approach should be applicable to patients with diabetes and concurrent AF to reduce diabetes-related complications. Adherence to such an integrated care approach has been associated with improved clinical outcomes (32) and has been recommended in guidelines (33).

Limitations

Several limitations need to be considered when interpreting the findings of this study. First, because of the retrospective study design, we cannot confirm a causal relationship between concurrent AF and diabetes-related complications. Although PS matching was used to reduce confounding factors and falsification analysis was performed to check for significant confounding factors between the study groups, residual bias cannot be entirely ruled out. Second, undetected complications may have existed among the study population before the follow-up started. A sensitivity analysis was performed to address this issue, and similar results were obtained when the study outcome was followed up for one year after the index health checkup. Third, the accuracy of the operational definitions of diabetes and diabetes-related complications may be a concern. Although a previous study has validated the definitions of macrovascular complications (34) and some studies used similar purposes for diabetic retinopathy, diabetic nephropathy, and diabetic foot (14,35–39), the accuracy of outcome definitions may vary across different populations. Regarding diabetic nephropathy, other causes, such as hypertension and glomerular nephropathy, cannot be excluded. Fourth, AF may have been undetected among patients in the non-AF group because of its paroxysmal nature. Some individuals in the non-AF group may have developed new-

onset AF during the follow-up period. Fifth, the study used data obtained between 2009 and 2012. Therefore, patients may not have received up-to-date, contemporary management of diabetes and AF, with limited use of newer antihyperglycemic drugs and oral anticoagulants. We especially acknowledge that the relatively low rate of oral anticoagulant use among patients with AF may impact our results' interpretability. Sixth, even though we performed PS matching, the differences in the covariates between the study groups may have been confounders. Seventh, adjusting diabetes durations may not have fully balance the severity and control of diabetes between the study groups. Eighth, there could have been potential confounding effects due to catheter ablation for AF during the follow-up. Finally, the NHIS database used in the study lacked laboratory values, including HbA_{1c} levels and AF burden, which prevented the evaluation of the dose-response relationship between AF burden and the risks of study outcomes. In summary, future studies are needed to address these limitations and achieve a more comprehensive understanding of the association between concurrent AF and diabetes-related complications.

In conclusion, among patients with diabetes, concurrent AF was associated with increased risks for diabetes-related macrovascular complication, diabetic nephroparhy, and diabetic foot. Such patients require a more holistic and integrated care management plan to reduce the risk of adverse outcomes.

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