**Accumulated hypertension burden on the risk of incident atrial fibrillation in patients with diabetes mellitus: A nationwide population-based study**

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**Abstract**

**Background:** Patients with diabetes mellitus have an increased risk of incident strial fibrillation (AF). Among the modifiable risk factors of AF, the effect of accumulated hypertension burden on the risk of AF remains less known in patients with diabetes. We aimed to study the relationship between accumulated hypertension burden and incident AF in patients with diabetes.

**Methods:** We evaluated 526384 patients with diabetes who underwent 3 consecutive health examinations between 2009 and 2012 from the Korean National Health Insurance Service. Hypertension burden was calculated by assigning points to each stage of hypertension in each health examination during total 3 health examinations: 1 for stage 1 hypertension [systolic blood pressure (SBP) 130-139 mmHg and diastolic BP (DBP) 80-89 mmHg], 2 for stage 2 hypertension (SBP 140-159 mmHg and DBP 90-99 mmHg), and 3 for stage 3 hypertension (SBP≥160 mmHg or DBP≥100 mmHg). The subjects were categorized into 10 groups of hypertension burden (0-9). Among the 10 groups, 9 groups excluding the reference group were regrouped into 3 subgroups: 1 to 3, 4 to 6, and 7 to 9.

**Results:** During a mean follow-up duration of 6.7±1.7 years, AF was newly diagnosed in 18,561 (3.5%) subjects (mean age XXX; x% female; incidence rate 5.3 per 1000 person-year). Compared to patients with hypertension burden 0, those with hypertension burden 1 to 9 showed a progressively increasing risk of incident AF: 6%, 11%, 16%, 24%, 28%, 41%, 46%, 57%, and 67% respectively. Regrouped 4 groups of 1 to 3, 4 to 6, and 7 to 9 showed increased risks by 10%, 26%, and 45%, respectively, when compared to hypertension burden 0.

**Conclusion:** Accumulated hypertension burden was associated with an increased risk of incident AF in diabetic patients. Strict BP control should be emphasized in managing patients with diabetes.

**Introduction**

Currently, 1 in 11 adults suffer from diabetes mellitus (DM) globally and the affected population is expected to rise to 700 million by 2045.1, 2 Also, deaths due to diabetes have doubled since 1990.3 Among the various causes of mortality in diabetes, cardiovascular disease is estimated to be account for one-third of deaths, mainly due to coronary artery disease and stroke.4 Thus, managing cardiovascular risk factors is essential in reducing the mortality and morbidity associated with diabetes.

Amongst diabetic patients, the presence of hypertension or atrial fibrillation (AF) is associated with an increased risk of complications including stroke.5-9 Furthermore, the diabetic population exhibits a higher risk of AF when compared to the subjects without diabetes.10, 11 Indeed, the combination of diabetes and the presence of hypertension leads to an even higher prevalence of AF, up to three fold, when compared to non-diabetic subjects.10 One previous study proposed a predictive model for AF in hypertensive diabetic patients with acceptable performance.12 However, these studies have primarily focused on the association between baseline hypertension at baseline and the incidence of AF.10-14 The impact of accumulated hypertension burden on the risk of AF in diabetes patients has never been previously explored.

In this study, we aimed to study the relationship between accumulated hypertension burden and incident AF in patients with diabetes, using a large nationwide population-based cohort study.

**Methods**

This study used the nationwide claims database from the Korean National Health Insurance Service (NHIS). The NHIS covers the whole population residing in South Korea. The NHIS database consists of demographic variables, mortality data, medical expenses, diagnoses encoded by the *International Classification of Disease, Tenth Revision of Clinical Modification* (ICD-10-CM), use of inpatient and outpatient services, and prescription records.15 Furthermore, National Health Screening Program for chronic diseases targets those over 19-year-old and contains data on physical examinations, laboratory results, chest radiographs and self-reporting questionnaires.16

This study was conducted according to the Declaration of Helsinki. The data used in this study were anonymized, and thus the study was exempted from the institutional review board (IRB) review of the Seoul National University Hospital (IRB no. E-2204-040-1314). Also, the data from NHIS were all deidentified, and the acquisition of the informed consent was not feasible. The use of the NHIS database from 2009 to 2012 was authorized in 2022.

*Study Population*

The overview of the patient flow is depicted in **Figure S1.** The subjects with diabetes mellitus who received a National Health Insurance Corporation (NHIC) health examination between January 1, 2009 and December 31, 2012, were screened for the study (n = 2,746,078). Subjects with ages below 40 were excluded (n = 191,249) and those who underwent 3 consecutive biannual health examinations, including the index health examination were identified (n = 550,044). We excluded those with prevalent AF before enrollment.

*Definition of accumulated hypertension burden*

During the health examination, the brachial BP was measured by a trained clinician in the sitting position after at least 5 minutes of rest by using either sphygmomanometers or oscillometers with a cuff of appropriate size. 17, 18 The BP measured at each health examination was classified into 4 categories of ‘no hypertension’ (SBP<130 mmHg and DBP<80 mmHg), stage 1 hypertension (SBP 130-139 mmHg and DBP 80-89 mmHg), stage 2 hypertension (SBP 140-159 mmHg and 90-99 mmHg), and stage 3 hypertension (SBP≥160 mmHg or DBP≥100 mmHg) consistent with previous hypertension guidelines.19, 20 We used the basic hypertension definitions from the 2017 ACC guideline for high BP and divided stage 2 hypertension into 2 groups of stage 2 (SBP 140-159 mmHg and 90-99 mmHg) and stage 3 (SBP≥160 mmHg or DBP≥100 mmHg) for further detailed evaluation of hypertension burden.

To quantify hypertension burden, we used semiquantitative scoring system for the BP measured at each health examination: 0 point for no hypertension, 1 point for stage 1 hypertension, 2 points for stage 2 hypertension, and 3 points for stage 3 hypertension. As a result, the subjects were categorized into 10 groups of hypertension burden (0-9) after 3 consecutive health examinations. Among the 10 groups, 9 groups except the reference group (group 0) were regrouped into 3 subgroups: 1’ (1 to 3), 2’ (4 to 6), and 3’ (7 to 9) (**Figure 1**).

*Covariates*

The baseline demographic information and comorbidities defined by ICD-10-CM codes, prescribed drug usage (antihypertensive medication and antidiabetic medication), and laboratory results from health examination is described in **Table 1**. The detailed definition of inclusion and exclusion criteria (AF, hypertension, diabetes mellitus) comorbidities (chronic kidney disease, dyslipidemia, heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease), health behavior (smoking, alcohol consumption, regular exercise), and household income are listed in **Supplementary Table S1**. For the antihypertensive medications, thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker were reviewed. For the antidiabetic medication, sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, and insulin were examined. All covariates were evaluated at the last (index, third) health examination with comorbidities assessed a year prior to index health examination. The general health examination values of SBP, DBP, body mass index, waist circumference was used. The laboratory results consisted of estimated glomerular filtration rate (eGFR), fasting glucose, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).21

*Study outcomes and follow-up*

During the follow-up period, incident AF was assessed as a primary outcome. AF was defined as the diagnosis of related ICD-10-CM codes (I48; AF and atrial flutter) for the first time during at least two different outpatient clinic visits or admission or death.22 The index date was the last (third) health examination. The subjects were followed from index date until the incident AF, disqualification from the NHIS (immigration or death), or end of the study (December 31, 2018) whichever came first.

*Statistical analysis*

In the baseline characteristics, continuous variables are presented as mean ± standard deviation (SD) and categorical variables as numbers and percentages. The comparison of baseline characteristics among different accumulated hypertension burden group was performed with a linear trend test using a generalized linear model for continuous variables, chi-square test and the Cochran-Armitage trend test for categorical variables. The AF incidence rate (IR) was calculated by dividing the incident AF events by1000 person-years at risk. For the survival analysis, Kaplan-Meier method draw the cumulative incidence of AF in relation to the accumulated hypertension burden. Cox proportional hazards regression model was used to evaluate the hazard ratio (HR) and 95% confidence intervals. A total of five stepwise Cox analysis models with adjustment of various combination of covariates were performed as follows: (i) unadjusted model (model 1); (ii) model adjusted for age and sex (model 2); (iii) model adjusted for age, sex, comorbidities (chronic kidney disease, dyslipidemia, heart failure, prior myocardial infarction, prior stroke, smoking, alcohol consumption, regular exercise, and low income (model 3); (iv) model 3 and addition of diabetes duration over 5 years, insulin usage, more than 3 oral anti-diabetic medications (model 4); (v) model 4 and addition of SBP, fasting glucose, total cholesterol, and BMI at the index health examination (model 5).

Subgroup analyses were performed according to age (<65 and ≥65 years), sex, the presence of CKD, prior MI or stroke, insulin usage, more than 3 oral anti-diabetic medications, diabetes duration over 5 years, and anti-hypertensive medication.

Statistical significance of p <0.05 was used. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

**Results**

A total of 514,967 subjects were included in the final study population. The subjects were categorized into ten groups and then regrouped into four groups. Of the whole cohort, the 10 groups of accumulated hypertension burden constituted 9.7% (n=50840), 14.2% (n=74963), 17.8% (n=93832), 18.7% (n=98354), 15.2% (n=79871), 11.3% (n=59612), 7.1% (n=37157), 3.9% (n=20370), 1.6% (n=8374), and 0.6% (n=3011) patients, respectively. Baseline characteristics according to the 4 subgroups is described in **Table 1** and when divided into the 10 subgroups is described in **Supplementary Table S2**.

In the 4 subgroups, the subjects in higher accumulated hypertension burden group were older but the prevalence of comorbidities did not show a linear trend. With higher accumulated hypertension burden, there was more prevalent heavy alcohol consumption, with less regular exercise and higher low-income population. Those with higher accumulated hypertension burden were more likely to receive anti-hypertensive medications, while the prescription of oral anti-diabetic medications or insulin and the proportion of patients with longer diabetes duration over 5 years were less common. Also, higher accumulated hypertension burden groups had higher mean BP, BMI, and WC at the index health examination. Laboratory results showed lower eGFR and higher fasting glucose, total cholesterol, triglyceride in higher hypertension burden subgroups.

*Risk of incident AF according to accumulated hypertension burden*

During a mean follow-up duration of 6.7 (SD 1.7) years, AF was newly diagnosed in 18,561 subjects (3.5% of total population; incidence rate of 5.3 per 1000 person-year). The IR and HR both increased with increasing accumulated hypertension burden (**Supplementary Tables S3** and **S4**). The cumulative incidence curves for AF according to hypertension burden are shown in **Figure 2**.Compared to patients with hypertension burden 0, those with hypertension burden 1 or higher showed the higher risk of AF.

Increasing AF risk was seen in accumulated hypertension burden based on ten subgroups, as follows: 6%, 11%, 16%, 24%, 28%, 41%, 46%, 57%, and 67%, respectively (*P* <0.001). When the study population was subgroups into four according to hypertension burden (hypertension burden 0, 1 to 3 [group 1’], 4 to 6 [group 2’], and 7 to 10 [group 3’]), increased AF risks were observed by 10%, 26%, and 45% in group 1’, 2’, and 3’, respectively, when compared to those with hypertension burden 0 (*P* <0.001). The associations between the accumulated hypertension burden and the risk of incident AF by adjusted HR (model 5) are presented in **Figure 3**.

*Subgroup analysis*

The results of subgroup analyses is shown in **Table 2.**  AF incidence was higher in the subgroups of age over 65 years old, CKD, prior MI or stroke, insulin use, DM duration over 5 years, and those with antihypertensive medication. In the subgroup with patients with 3 or more oral anti-diabetic medications and with insulin who were considered having more advanced diabetes, consistently with the main results were observed. The severity of diabetes mellitus as presumed by the prescription of more than 3 oral anti-diabetic medications or insulin did not show a significant interaction.

**Discussion**

In this study, our principal findings are as follows: (1) diabetes patients with higher accumulated hypertension burden had an increased risk of incident AF; and (2) accumulated hypertension burden showed a positive correlation with the risk of AF in a diabetic population, regardless of the severity of the diabetes. As far as we are aware, this is the first study to evaluate the risk of incident AF in diabetes patients with accumulated hypertension burden.

Diabetes is one of the most common chronic medical conditions affecting one in eleven adults globally.1 Subjects with diabetes are at higher risk of major cardiovascular adverse events and mortality compared to non-diabetic subjects.23 Indeed, they are more likely to develop AF by atrial structural remodeling and adrenergic activation and have even higher risk of major coronary events, stroke, heart failure and mortality when present in combination with AF. 24-27 Diabetic subjects with AF also suffer worse AF symptom burden and lower quality of life.27 As cumulative exposure to diabetes status itself increases the risk of AF by 3% for each additional year,28, 29 it is important to control other modifiable risk factors of AF in diabetic patients.

Hypertension is one of the common modifiable risk factors which affects the pathogenesis, management, and prognosis of AF.30, 31 Hypertension is responsible for more than one fifth of incident AF and showd a linear increase of risk when the exposure is accumulated.17, 32, 33 In diabetic patients, hypertension affects over two-thirds of patients34, and he coexistence of hypertension in diabetic patients increases the risk of AF 3-fold.10 However, the latter study was a cross-sectional observational study which focused on the presence or absence of baselin hypertension.10 The accumulated effect of hypertension on AF development in diabetes patients have not been previously evaluated.

Although the pathophysiology of AF is still under investigation, there are possible explanations for the association between hypertension and AF. In animal models, hypertension was associated with atrial remodeling, especially fibrosis, and higher AF inducibility30, 35-37 38. Long-term exposure to hypertension is also associated with left ventricular hypertrophy, leading to increased left atrial pressure and subsequent atrial enlargement.39-42 Such structural remodeling leads to the increased incidence of AF in dose-dependent response to cumulative hypertension burden, as shown in our study and by others.32 As such change in left ventricular hypertrophy can be prevented or even improved with intensive BP control and antihypertensive medications43, 44, strict BP control should lower the incidence of AF in diabetic patients.

In the subgroup analyses, the subjects with antihypertensive medication showed higher incidence of AF but did not show significant interaction, unlike the previous study done on the general population.32 This difference could be caused by the effect of diabetes outweighing hypertension on the AF incidence.10 Another interesting result in the subgroup analyses was that the severity of diabetes, presumed by insulin usage 45, which did not show significant interaction on AF risk. Albeit the increased absolute AF incidence in the insulin group (as was seen in the previous studies46-48), accumulated hypertension burden had similar impact on the risk of AF in diabetic patients regardless of the insulin usage. Thus, strict BP control is important in all diabetic patients irrespective of the severity of the diabetes.

In this study, the accumulated hypertension burden persistently showed increased AF risk regardless of the known duration of diabetes. Accumulated diabetes burden is known to be associated with the increased AF incidence by 3% per each additional year28, 29, so a long-term comprehensive treatment plan on the evaluation and management of diabetes and hypertension is needed to lower AF risk on patients with longer diabetes duration. This is aligned with the current approach to characterization and evaluation of AF patients [ref], followed by a holistic or integrated care approach to AF management [ref]. Such integrated care management has been associated with improved clinical outcomes [ref] and recommended in guidelines [ref].

*Limitations*

This study has several limitations. First, our study used I48 as a definition of AF. Using ICD-10-CM codes in AF diagnosis may be less accurate than reviewing the actual electrocardiogram. However, AF definition using I48 was previously validated using 628 subjects with a positive predictive value as high as 94.1%.49 Second, this study focused only on hypertension burden and did not distinguish subjects in pre-hypertensive status from normal BP subjects. As prehypertensive status is also associated with increased risk of AF50, further studies are needed to define the association between accumulated prehypertension burden and the risk of AF in diabetes patients. Lastly, we studied the Korean population, which is considered homogenous, hence a limitation in generalizability to other multi-ethnic populations.

**Conclusion**

Accumulated hypertension burden was associated with an increased risk of incident AF in diabetic patients. Strict BP control should be emphasized in managing patients with diabetes, helping reduce the risk of AF-related complications in this population.

**Conflict of Interest**

EKC: Research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd, Medtronic, Samjinpharm, Seers Technology, and Skylabs. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were received personally by any author.

**Author Contributions**

Eue‑Keun Choi coordinated the whole study as the principal investigator. Seung-Woo Lee and Kyung‑Do Han oversaw the statistics. JungMin Choi and So‑Ryoung Lee prepared the original draft with support from Hyo-Jeong Ahn, Soonil Kwon, HuiJin Lee, and MinJu Han. Seil Oh and Gregory Y. H. Lip supervised the findings of this work.

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**FIGURE LEGENDS**

**Figure 1.** **Study design**

Abbreviation: BP, blood pressure; Gr, grade; HTN, hypertension; Ref, reference.

**Figure 2. Association between cumulative hypertension burden and hazard ratio of incident AF in subjects with diabetes mellitus by (A) group of ten and (B) group of four.**

Abbreviation: CI, confidence interval; HTN, hypertension.

**Figure 3.** **Cumulative incidence curves of AF stratified by hypertension burden by (A) group of ten and (B) group of four.**

Abbreviation: AF, atrial fibrillation; CI, confidence interval; HTN, hypertension.