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

JungMin Choi, MD1†; So‑Ryoung Lee, MD, PhD1†; Eue‑Keun Choi, MD, PhD1,2\*; HuiJin Lee, MD1; MinJu Han, MD1; Hyo-Jeong Ahn, MD1; Soonil Kwon, MD1; Seung-Woo Lee, BSc3; Kyung‑Do Han, PhD4; Seil Oh, MD, PhD1,2; Gregory Y. H. Lip, MD2,5,6

1Division of cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

2Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

3Department of Medical Statistics, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea

4Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea

5Liverpool Center for Cardiovascular Science, University of Liverpool and Liverpool Chest & Heart Hospital, Liverpool, United Kingdom

6Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

†These authors have contributed equally to this work and share the first authorship

**\* Correspondence:**

Eue-Keun Choi, MD, PhD

Professor of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital,

101 Daehak‐ro, Jongno‐gu, Seoul 03080, Republic of Korea. Email: choiek17@snu.ac.kr

**Keywords:** atrial fibrillation, diabetes mellitus, hypertension, burden

**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.

**Funding**

This work was supported in part by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (Project Number: HI20C1662, 1711138358, KMDF\_PR\_20200901\_0173), and by a grant from the Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC21C0028).

**Acknowledgments**

We thank the NHIS for the approval of the data usage.

**References**

1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. Feb 2018;14(2):88-98. doi:10.1038/nrendo.2017.151

2. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. Nov 2019;157:107843. doi:10.1016/j.diabres.2019.107843

3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. Dec 15 2012;380(9859):2095-128. doi:10.1016/s0140-6736(12)61728-0

4. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. Jun 8 2018;17(1):83. doi:10.1186/s12933-018-0728-6

5. Gillett M, Davis WA, Jackson D, Bruce DG, Davis TM. Prospective evaluation of carotid bruit as a predictor of first stroke in type 2 diabetes: the Fremantle Diabetes Study. *Stroke*. Sep 2003;34(9):2145-51. doi:10.1161/01.Str.0000087360.91794.11

6. Abu-Lebdeh HS, Hodge DO, Nguyen TT. Predictors of macrovascular disease in patients with type 2 diabetes mellitus. *Mayo Clin Proc*. Jul 2001;76(7):707-12. doi:10.4065/76.7.707

7. Davis TM, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. *Arch Intern Med*. May 24 1999;159(10):1097-103. doi:10.1001/archinte.159.10.1097

8. Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke*. Jan 1996;27(1):63-8. doi:10.1161/01.str.27.1.63

9. McFarlane SI, Sica DA, Sowers JR. Stroke in patients with diabetes and hypertension. *J Clin Hypertens (Greenwich)*. May 2005;7(5):286-92; quiz 293-4. doi:10.1111/j.1524-6175.2005.04379.x

10. Ostgren CJ, Merlo J, Råstam L, Lindblad U. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. *Diabetes Obes Metab*. Sep 2004;6(5):367-74. doi:10.1111/j.1462-8902.2004.00358.x

11. Seyed Ahmadi S, Svensson AM, Pivodic A, Rosengren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol*. Jan 18 2020;19(1):9. doi:10.1186/s12933-019-0983-1

12. Abellana R, Gonzalez-Loyola F, Verdu-Rotellar JM, et al. Predictive model for atrial fibrillation in hypertensive diabetic patients. *Eur J Clin Invest*. Dec 2021;51(12):e13633. doi:10.1111/eci.13633

13. Rattani A, Claxton JS, Ali MK, Chen LY, Soliman EZ, Alvaro A. Association and impact of hypertension defined using the 2017 AHA/ACC guidelines on the risk of atrial fibrillation in The Atherosclerosis Risk in Communities study. *BMC Cardiovasc Disord*. Nov 26 2019;19(1):262. doi:10.1186/s12872-019-1259-0

14. Alves-Cabratosa L, García-Gil M, Comas-Cufí M, et al. Diabetes and new-onset atrial fibrillation in a hypertensive population. *Ann Med*. 2016;48(3):119-27. doi:10.3109/07853890.2016.1144930

15. Cheol Seong S, Kim Y-Y, Khang Y-H, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. *International Journal of Epidemiology*. 2016;46(3):799-800. doi:10.1093/ije/dyw253

16. Lee W-C, Lee S-Y. National Health Screening Program of Korea. *jkma*. 05 2010;53(5):363-370. doi:10.5124/jkma.2010.53.5.363

17. Lee S-R, Choi Y-J, Choi E-K, et al. Blood Pressure Variability and Incidence of New-Onset Atrial Fibrillation. *Hypertension*. 2020;75(2):309-315. doi:doi:10.1161/HYPERTENSIONAHA.119.13708

18. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252. doi:doi:10.1161/01.HYP.0000107251.49515.c2

19. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Journal of the American College of Cardiology*. 2018;71(19):e127-e248. doi:doi:10.1016/j.jacc.2017.11.006

20. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6):1334-1357. doi:doi:10.1161/HYPERTENSIONAHA.120.15026

21. Park CS, Han K-D, Choi E-K, et al. Lifestyle is associated with atrial fibrillation development in patients with type 2 diabetes mellitus. *Scientific Reports*. 2021/02/25 2021;11(1):4676. doi:10.1038/s41598-021-84307-5

22. Choi EK. Cardiovascular Research Using the Korean National Health Information Database. *Korean Circ J*. Sep 2020;50(9):754-772. doi:10.4070/kcj.2020.0171

23. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. Mar 5 2019;139(10):e56-e528. doi:10.1161/cir.0000000000000659

24. Kato T, Yamashita T, Sekiguchi A, et al. AGEs-RAGE system mediates atrial structural remodeling in the diabetic rat. *J Cardiovasc Electrophysiol*. Apr 2008;19(4):415-20. doi:10.1111/j.1540-8167.2007.01037.x

25. Otake H, Suzuki H, Honda T, Maruyama Y. Influences of autonomic nervous system on atrial arrhythmogenic substrates and the incidence of atrial fibrillation in diabetic heart. *Int Heart J*. Sep 2009;50(5):627-41. doi:10.1536/ihj.50.627

26. Du X, Ninomiya T, de Galan B, et al. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur Heart J*. May 2009;30(9):1128-35. doi:10.1093/eurheartj/ehp055

27. Echouffo-Tcheugui JB, Shrader P, Thomas L, et al. Care Patterns and Outcomes in Atrial Fibrillation Patients With and Without Diabetes: ORBIT-AF Registry. *J Am Coll Cardiol*. Sep 12 2017;70(11):1325-1335. doi:10.1016/j.jacc.2017.07.755

28. Dublin S, Glazer NL, Smith NL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. *J Gen Intern Med*. Aug 2010;25(8):853-8. doi:10.1007/s11606-010-1340-y

29. Yang S, Choi EK, Han KD, et al. Risk of Atrial Fibrillation in Relation to the Time Course of Type 2 Diabetes Mellitus and Fasting Blood Glucose. *Am J Cardiol*. Dec 15 2019;124(12):1881-1888. doi:10.1016/j.amjcard.2019.09.009

30. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation*. Aug 8 2017;136(6):583-596. doi:10.1161/circulationaha.116.023163

31. Dzeshka MS, Shantsila A, Shantsila E, Lip GYH. Atrial Fibrillation and Hypertension. *Hypertension*. Nov 2017;70(5):854-861. doi:10.1161/hypertensionaha.117.08934

32. Lee SR, Park CS, Choi EK, et al. Hypertension Burden and the Risk of New-Onset Atrial Fibrillation: A Nationwide Population-Based Study. *Hypertension*. Mar 3 2021;77(3):919-928. doi:10.1161/hypertensionaha.120.16659

33. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. Apr 12 2011;123(14):1501-8. doi:10.1161/circulationaha.110.009035

34. Sabuncu T, Sonmez A, Eren MA, et al. Characteristics of patients with hypertension in a population with type 2 diabetes mellitus. Results from the Turkish Nationwide SurvEy of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus (TEMD Hypertension Study). *Prim Care Diabetes*. Apr 2021;15(2):332-339. doi:10.1016/j.pcd.2020.11.001

35. Lau DH, Mackenzie L, Kelly DJ, et al. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. *Heart Rhythm*. Sep 2010;7(9):1282-90. doi:10.1016/j.hrthm.2010.05.010

36. Lau DH, Mackenzie L, Kelly DJ, et al. Short-term hypertension is associated with the development of atrial fibrillation substrate: a study in an ovine hypertensive model. *Heart Rhythm*. Mar 2010;7(3):396-404. doi:10.1016/j.hrthm.2009.11.031

37. Lau DH, Shipp NJ, Kelly DJ, et al. Atrial arrhythmia in ageing spontaneously hypertensive rats: unraveling the substrate in hypertension and ageing. *PLoS One*. 2013;8(8):e72416. doi:10.1371/journal.pone.0072416

38. Pluteanu F, Heß J, Plackic J, et al. Early subcellular Ca2+ remodelling and increased propensity for Ca2+ alternans in left atrial myocytes from hypertensive rats. *Cardiovasc Res*. Apr 1 2015;106(1):87-97. doi:10.1093/cvr/cvv045

39. Mosterd A, D'Agostino RB, Silbershatz H, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. *N Engl J Med*. Apr 22 1999;340(16):1221-7. doi:10.1056/nejm199904223401601

40. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med*. Jul 1969;71(1):89-105. doi:10.7326/0003-4819-71-1-89

41. Okin PM, Gerdts E, Wachtell K, et al. Relationship of left atrial enlargement to persistence or development of ECG left ventricular hypertrophy in hypertensive patients: implications for the development of new atrial fibrillation. *J Hypertens*. Jul 2010;28(7):1534-40. doi:10.1097/hjh.0b013e328338c20e

42. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size. The Framingham Heart Study. *Hypertension*. Jun 1995;25(6):1155-60. doi:10.1161/01.hyp.25.6.1155

43. Soliman EZ, Ambrosius WT, Cushman WC, et al. Effect of Intensive Blood Pressure Lowering on Left Ventricular Hypertrophy in Patients With Hypertension: SPRINT (Systolic Blood Pressure Intervention Trial). *Circulation*. Aug 1 2017;136(5):440-450. doi:10.1161/circulationaha.117.028441

44. Dernellis JM, Vyssoulis GP, Zacharoulis AA, Toutouzas PK. Effects of antihypertensive therapy on left atrial function. *J Hum Hypertens*. Dec 1996;10(12):789-94.

45. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. Jan 2021;44(Suppl 1):S111-s124. doi:10.2337/dc21-S009

46. Chen HY, Yang FY, Jong GP, Liou YS. Antihyperglycemic drugs use and new-onset atrial fibrillation in elderly patients. *Eur J Clin Invest*. May 2017;47(5):388-393. doi:10.1111/eci.12754

47. Liou YS, Yang FY, Chen HY, Jong GP. Antihyperglycemic drugs use and new-onset atrial fibrillation: A population-based nested case control study. *PLoS One*. 2018;13(8):e0197245. doi:10.1371/journal.pone.0197245

48. Fauchier G, Bisson A, Bodin A, et al. Glucose-lowering drug use and new-onset atrial fibrillation in patients with diabetes mellitus. *Diabetologia*. Nov 2021;64(11):2602-2605. doi:10.1007/s00125-021-05551-y

49. Lee SS, Ae Kong K, Kim D, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. *European Heart Journal*. 2017;38(34):2599-2607. doi:10.1093/eurheartj/ehx316

50. Lee SS, Ae Kong K, Kim D, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. *Eur Heart J*. Sep 7 2017;38(34):2599-2607. doi:10.1093/eurheartj/ehx316

**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.