**Effect of hypertension duration and blood pressure level on ischemic stroke risk in atrial fibrillation: Nationwide data covering the entire Korean population**

Tae-Hoon Kim, MD\*; 1 Pil-Sung Yang, MD\*; 2 Hee Tae Yu, MD; 1 Eunsun Jang, MS;1 Hyejung Shin, MS; 3 Ha Yan Kim, MS; 3 Jae-Sun Uhm, MD; 1 Jong-Youn Kim, MD; 1 Jung-Hoon Sung;2 Hui-Nam Pak, MD; 1 Moon-Hyoung Lee, MD; 1 Boyoung Joung, MD†;1 Gregory Y.H. Lip, MD† 1, 4, 5

From the Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea 1, Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea 2, Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea 3, and Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom 4 and Liverpool Centre for Cardiovascular Science, University of Liverpool, United Kingdom 5

[\*These two authors contributed equally to this work] [†Joint senior authors]

Cover Title: Hypertension and ischemic stroke in AF

Word count: 4,720

Disclosures: none

**Address for correspondence:**

Boyoung Joung, MD. Gregory Y.H. Lip, MD.

50 Yonseiro, Seodaemun-gu, Institute of Cardiovascular Sciences,

Seoul, Republic of Korea 120-752 University of Birmingham, Birmingham

Phone: +82-2-2228-8460 England, United Kingdom

Fax: +82-2-393-2041

E-mail: [cby6908@yuhs.ac](mailto:cby6908@yuhs.ac) E-mail: [g.y.h.lip@bham.ac.uk](mailto:g.y.h.lip@bham.ac.uk)

**Introduction**

Hypertension, which is considered as the most important risk factor for stroke in the general population, is the most common comorbidity in patients with atrial fibrillation (AF), and is prevalent in approximately 80% to 90% of subjects with AF enrolled in recent clinical trials.1-3 Diagnosed hypertension is an important risk factor for ischemic stroke in patients with AF, and is incorporated in the CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischaemic attack (doubled), vascular disease, age 65 to 74, female] stroke risk stratification score which is widely used in most guidelines for stroke prevention in AF.4,5

Poor blood pressure (BP) control seems to worsen outcomes in AF via left ventricular diastolic dysfunction [where associated HF is present, this is called “heart failure with preserved ejection fraction (HFpEF)”], left atrial overload and remodelling.6-10 However, most studies have reported increased risk of stroke in patients with AF who have a history of hypertension (regardless of blood pressure level), and only few studies with relatively small sample size have reported the significance of systolic BP (SBP) level ≥140 mmHg11 or ≥160mmHg12-14 in patients with AF, rather than the history of hypertension, as a risk factor for stroke in AF. Recently, our group have suggested the optimal BP target in patients with AF, which may lower the risk of ischemic stroke as well as cardiovascular event or death.15 However, there are a paucity of data investigating the association between duration of hypertension and risk of stroke, and it is unclear if the risk of stroke in patients with long duration of hypertension, but with well-controlled BP, have a similar risk of ischemic stroke compared to AF patients without hypertension. Moreover, AF4,5 and hypertension16-18 guidelines do not have specific recommendations regarding SBP control or considering the duration of hypertension in patients with AF, particularly for stroke prevention. Therefore, a clearer understanding of the association of SBP level and duration of hypertension with the risk of stroke is needed to improve the predictive ability of the risk score among hypertensive AF patients. Our objective was to investigate the associations of duration of hypertension and blood pressure levels with the risk of stroke in patients with AF from a nationwide cohort study.

**Subjects and Methods**

This study is based on the national health claims database established by the National Health Insurance Service (NHIS) of Republic of Korea,19,20 and was approved by the Institutional Review Board of Yonsei University Health System (4-2016-0179). Informed consent was waived. Further details are presented in Supplementary material.

This study enrolled 246,459 oral anticoagulant-naïve non-valvular AF patients from NHIS database. Details are presented in Figure 1 and Supplementary material.

*Hypertension, Ischemic stroke and Baseline comorbidities*

Hypertension was defined as the combination of previous hypertension diagnosis (ICD-10 codes) and use of 1 or more antihypertensive drugs. Hypertension onset date for duration calculations was determined by using information on the first date of hypertension diagnosis. The comorbidities were defined at the time of AF diagnosis, and assessed annually during the follow period. The study endpoint was ischemic stroke, which was defined with any admission diagnosis of ischemic stroke with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging.21 The detailed definitions of comorbidities are presented in Supplementary Table 1.

*Statistical analysis*

For the duration of hypertension analysis, the duration was categorized as < 3 years, 3 to 5 years, and ≥ 5 years. To assess the effect of hypertension duration and SBP levels on stroke risk, we analyzed baseline SBP levels at the time of AF diagnosis in Model 1. To investigate the effect of long-term BP control on the association between hypertension duration and risk of ischemic stroke (Model 2), we included patients who had more than two available previous health check-up data between the time of hypertension diagnosis and that of AF diagnosis, and calculated average SBP levels. Further details, including SBP analyses, are described in Supplemental material.

**Results**

***Baseline characteristics***

Patient baseline characteristics were presented in Table 1. A total of 205,177 (83.2%) patients had history of diagnosed hypertension, and included in the duration analysis: 40.4% patients with duration <3 years, 15.0% with duration 3 to 5 years, and 44.6% with duration ≥5 years at baseline. The proportion of patients’ baseline SBP level was as follows: (i) 16.8% non-hypertensive (SBP <140 mmHg); (ii) 60.4% well controlled hypertension (SBP<140 mmHg); (iii) 17.3% uncontrolled hypertension with SBP 140-159 mmHg; and (iv) 5.5% uncontrolled hypertension with SBP ≥160 mmHg (Supplementary table 2).

***Duration of hypertension and ischemic stroke***

In the duration of hypertension analysis, there were 533,854 person-years (mean 0.72 ± 0.41 years/patient) data included in patients with AF. Duration of hypertension and ratios for ischemic stroke are presented in Table 2. When compared to non-hypertensive patients (3.33, 100 person-years [100PY]), all patients with hypertension showed higher ischemic stroke rates regardless of duration of hypertension (100PY, 6.97 in 0 to 3years, 10.82 in 3 to 5 years, 13.63 in ≥ 5years). In multivariable Cox models adjusted for clinical variables, hypertension duration of 0 to 3 years (adjusted hazard ratio [HR]: 1.32, 95% confidence interval [CI]: 1.24-1.42), 3 to 5 years (adjusted HR: 1.50, 95% CI: 1.38-1.64), and ≥ 5 years (adjusted HR: 1.52, 95% CI: 1.38-1.64) showed an increased adjusted risk of stroke, respectively (Table 2). Moreover, among hypertensive patients, compared with that of 0 to 3 years, hypertension duration 3 to 5 year and ≥ 5 years increased the risk of ischemic stroke with adjusted hazard ratios of 1.31 (95% CI: 1.25-1.38) and 1.40 (95% CI: 1.34-1.47), respectively.

Figure 2 demonstrates the adjusted HRs associated with duration of hypertension modeled as continuous variable using a cubic spline for the ischemic stroke. These analyses confirm an approximately linear dose–response relationship between the duration of hypertension and the risk of ischemic stroke. One-year increase in duration of hypertension continuously increased the adjusted risk of ischemic stroke until 7-years of hypertension (adjusted HR: 1.08, 95% CI: 1.07-1.09), and reached a plateau with adjusted HR of 1.6 (adjusted HR: 1.00, 95% CI: 0.09-1.02 after 7-years of hypertension duration).

When stratified by age subgroups, the risk of ischemic stroke continuously increased linearly with the increase of hypertension duration in subgroups of ages ≤ 55 and 55 to 64-years, and then reached plateau in subgroup aged 65 to 74 years and in those aged ≥ 75 years (Figure 3). Similar trends were observed in the competing-risk regression analyses for the all-cause mortality (Supplementary Table 4, Supplementary Figure 5).

***Duration of hypertension in different disease subgroups and sensitivity analyses***

Table 3 shows subgroup analyses and sensitivity analyses for the adjusted hazard ratios of 1-year ischemic stroke associated with duration of hypertension. In subgroup analyses, longer duration of hypertension increased the risk of ischemic stroke regardless of heart failure, diabetes mellitus, prior stroke/TIA, and chronic kidney disease. Particularly, the effect of hypertension duration on stroke risk was greater for the patients with heart failure, when compared to those without (P <0.01 for interaction). In sensitivity analyses, longer duration of hypertension increased the risk of ischemic stroke under the following conditions: after excluding patients with prior stroke/TIA history; after excluding patients with baseline comorbidities such as heart failure, diabetes, vascular disease, and CKD; after excluding patients with intracranial hemorrhage occurred during follow-up period; or after including systemic embolic event as an outcome.

***Duration of hypertension in different SBP levels***

Kaplan Meier analysis for crude rate of ischemic stroke according to baseline SBP levels (at the time of AF diagnosis) showed that patients with lower SBP < 120 mmHg at baseline had higher cumulative survival free of ischemic stroke than other SBP levels (log rank p<0.001) (Supplementary Figure 1). A 10-mmHg increase in SBP level increased the adjusted risk of stroke (adjusted HR: 1.06, 95% CI: 1.05-1.07) (Supplementary Figure 2).

Figure 4 shows the risk for ischemic stroke according to the duration of hypertension in patients with different baseline SBP categories (Model 1). In all subgroups with different baseline SBP levels, significantly increasing trends in stroke risk were observed with increasing duration of hypertension among hypertensive patients (all P values for trends <0.01). Moreover, the presence of hypertension (regardless of duration) was associated with higher risk of ischemic stroke compared to non-hypertensive patients (2.97 per 100PY). Hypertensive patients with duration ≥ 5 years and baseline SBP ≥160 mmHg showed adjusted HR of 2.25 for ischemic stroke (95% CI: 1.94-2.60, 19.16 per 100PY), whereas those with duration < 3 years and baseline SBP <120 mmHg showed adjusted HR of 1.36 (95% CI: 1.22-1.52, 6.38 per 100PY).

Improvement in the predictive ability of modified CHA2DS2-VASc, which was calculated using hypertension with duration ≥ 5 years and SBP ≥ 160 mmHg as two points, was compared with CHA2DS2-VASc score, and the area under ROC curve (AUC) of the modified CHA2DS2-VASc scoring system was improved from 0.647 to 0.648 (p<0.001). These improvements in the predictive ability of risk scoring schemes were also observed in the CHADS2 and the ATRIA score (Supplementary Table 3).

***Average SBP control levels before AF diagnosis***

Of the overall study population, 78.8% patients (194,108 out of 246,459) had at least two BP measurements before diagnosis of AF (between diagnosis of hypertension and AF), and average SBP values were used in the analyses (model 2, Figure 5). Results were similar with those using baseline SBP levels (model 1), and hypertensive patients with duration ≥ 5 years and pre-AF average SBP ≥160 mmHg showed adjusted HR of 1.95 for ischemic stroke (95% CI: 1.56-2.44, 20.44 per 100PY) when compared to non-hypertensive patients (3.17 per 100PY). However, in patients with pre-AF average of SBP <120 mmHg, patients with all hypertension duration categories showed no significant differences in adjusted hazard ratios for ischemic stroke (1.11 [0.97-1.28] for 0 to 3years, 1.03 [0.84-1.26] for 3 to 5years, 1.18 [1.00-1.39] for ≥5years) when compared to non-hypertensive patients.

***Change in the total number of anti-hypertensive medication and risk of stroke***

The risk of stroke according to the change in total number of BP medications (before the AF diagnosis date) was assessed. Total number of BP medications was reduced, not changed, and increased during the period from the hypertension diagnosis date to the AF diagnosis date in 31,320 (12.7%), 128,059 (51.9%), and 87,151 (35.4%) patients, respectively. Linear dose–response relationship between the duration of hypertension and the risk of ischemic stroke according to changes in the number of BP medication are presented in Supplementary Figure 3. The risk of stroke was increased in patients with stopped, reduced, or no-changed number of BP medication (probably in relation to insufficient BP control and non-adherence/non-persistence). In contrast, the effect of hypertension duration on the risk of stroke was relatively lower in patients with increased number of BP medications (which could mean aggressive adjustment of BP medication). Patients with increased numbers of BP medications had a lower risk of ischemic stroke than other patients.

**Discussion**

In this analysis of > 240,000 oral anticoagulant naïve AF patients in the entire Korean population, there are three major findings. First, one-year increase of hypertension duration continuously increased the adjusted risk of ischemic stroke (adjusted HR: 1.08, 95% CI: 1.07-1.09) until 7-years, and reached a plateau with adjusted HR of 1.6 (adjusted HR 1.00, 95% CI: 0.98-1.02 after 7 years of hypertension duration). The risk of ischemic stroke increased linearly with the increase of hypertension duration in patients younger than 65 years, whereas the risk reached plateau in patients aged 65 years or older. Second, in all baseline SBP groups, including those with well-controlled SBP (SBP <120mmHg or 120-139 mmHg), longer duration (≥ 3 years) of hypertension was associated with higher risk of ischemic stroke compared to shorter duration (< 3 years). Finally, in patients with strictly controlled SBP (pre-AF average SBP less than 120 mmHg), hypertension (even with long duration) was not associated with higher ischemic stroke risk when compared to non-hypertensive patients. Our study suggests that an increased duration of hypertension was associated with an increased risk of ischemic stroke even in patients with well controlled SBP level at the time of AF diagnosis and initial stroke risk stratification. However, the increased risk of ischemic stroke seen with long-term hypertension can be attenuated by continuously applied strict BP control before AF diagnosis.

***Duration of hypertension and the risk of ischemic stroke***

Patients with hypertension were at higher risk of ischemic stroke events compared to patients without hypertension, and importantly, the longer duration of hypertension had higher risk of ischemic stroke than shorter duration. On the other hand, several studies have reported that in diabetes, which is an important risk factor for ischemic stroke in AF, the longer estimated duration of the disease was strongly associated with an increase in adjusted rate of ischemic stroke.22,23 Ashburner et al.22 have shown that duration of diabetes is a more important predictor of ischemic stroke than glycemic control in patients who have diabetes and AF, suggesting the different mechanisms of ischemic stroke between AF and non-AF patients.

The mechanisms linking hypertension duration to an increased stroke risk are multifactorial. Long-standing hypertension, particularly if sub-optimally controlled, could lead to left ventricular hypertrophy, left atrial enlargement/fibrosis, and diastolic dysfunction, all of which may contribute to the increased burden of AF and consequently increased risk of ischemic stroke,6-10 as well as non-cardioembolic stroke.24

In this study, the risk of ischemic stroke after AF diagnosis increased linearly with the increase of SBP. However, interestingly, hypertension duration showed a linear dose-response relationship with plateau in patients except for those who were younger than 65 years old. This result has important clinical implication, as it suggests that in younger patients, longer duration of hypertension can increase the risk of stroke continuously if it is not strictly controlled.

***Effect of hypertension duration according to systolic blood pressure levels***

The longer duration of hypertension was associated with higher ischemic stroke risk, even in patients with well-controlled baseline SBP (SBP <120 mmHg or 120-139 mmHg) level at the time of AF diagnosis. This result suggests that, even if patients with first diagnosed AF have well controlled baseline SBP level and do not have no other risk factors for ischemic stroke, potential risk of stroke should not be overlooked in the initial stroke risk stratification if they have long duration of hypertension history. Although the CHA2DS2-VASc stroke risk score used in most AF guidelines includes a diagnosis of hypertension as a stroke risk factor,4,5 there is no specific definition on the duration of hypertension and stroke risk, given the lack or prior data regarding the association between hypertension duration and risk of ischemic stroke in AF, as well as cardiovascular risk. By including longer duration and higher SBP in modified CHA2DS2-VASc stroke, the predictive values of CHA2DS2-VASc score for ischemic stroke could be improved, particularly in hypertensive patients. It has important clinical implications, given that it is unclear (with different recommendations among international guidelines) whether OAC should be prescribed in young AF patient with no risk factor other than hypertension (therefore would be categorized as intermediate risk with CHA2DS2-VASc score 1 in males and 2 in females).

***Strict blood pressure control and the risk of stroke***

The 2017 AHA/ACC guidelines recently lowered the recommended threshold for the diagnosis of hypertension from ≥140/90 mmHg to ≥130/80 mmHg in the general population.18 However, all published guidelines do not have specific recommendations for blood pressure targets in patients with AF, especially for stroke prevention. Although longer duration of hypertension was associated with higher ischemic stroke risk, hypertension (even with long duration) was not associated with higher ischemic stroke risk in patients with strict SBP control who had pre-AF average SBP < 120 mmHg, compared to non-hypertensive patients. These results strongly suggest that the long-term effect of hypertension duration can be attenuated by long-term strict SBP control throughout the entire duration of hypertension. Moreover, in SBP analysis of current data set (Supplementary Figures 1 and 4), baseline SBP < 120 mmHg group showed significant benefit compared to baseline SBP 120–139 mmHg group. The result of this study suggests that AF patients with longer hypertension duration and/or uncontrolled SBP levels should be categorized as “high risk”, and that strict BP control over the entire duration of hypertension, combined with OAC, would be very important for reducing the risk of ischemic stroke.

***Limitations***

The present study has several limitations. Although administrative databases are increasingly used for clinical research, such studies are potentially susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition that we already validated in previous studies that used a Korean NHIS sample cohort.21,25-28 Because data regarding types of AF (paroxysmal vs. nonparoxysmal) were not available, we could therefore not investigate whether the effect of hypertension duration and/or SBP level differed according to types of AF. Since health examinations supported by the National Health Insurance System were performed in different hospitals and clinics, there was a lack of uniformity of BP measuring devices. Because this database study evaluated only the first-year ischemic stroke outcome after AF diagnosis, further evidence is required to establish the association between the duration of hypertension and long-term risk of ischemic stroke after AF diagnosis. Finally, there was no available information about ambulatory blood pressure monitoring data. Therefore, analyses of BP levels using this health examination data should be interpreted with caution; however, to overcome this, this study also analyzed 194,108 (78.8%) patients with at least two BP measurement before AF diagnosis. Despite these limitations, this study included the evaluation of longitudinal data from the *entire* Korean adult population. Therefore, our findings reflect the ischemic stroke risk of “real world” AF regarding the effect of hypertension duration and SBP levels on ischemic stroke in OAC naïve AF on nationwide scale.

**Conclusions**

The longer duration of hypertension before AF diagnosis was associated higher risk of ischemic stroke regardless of SBP levels at AF diagnosis. This long-term effect of hypertension duration can be attenuated by long-term strict SBP control throughout the entire duration of hypertension. The result of this study suggests that AF patients with longer hypertension duration, as well as uncontrolled SBP levels, should be categorized as ‘high risk’ and strict BP control with OAC would be important to reduce the risk of ischemic stroke.

**Sources of Funding**

This study was supported by a research grant from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2017R1A2B3003303), research grant from Development of Fundamental Technology Program through the National Research Foundation of Korea funded by Ministry of Science, ICT, & Future Planning (MSIP) (NRF-2017M3A9E8029724), and grants from the Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (HI16C0058, HI15C1200). This research was supported by a grant from Abbott Laboratories

**Disclosures**

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees were received personally.

JBY: Research fund from Abbort.

None of the other authors have any disclosures to make.

**References**

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, Committee R-LS, Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139-1151.

2. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, Committees A, Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981-992.

3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883-891.

4. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, Members AATF. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:e199-267.

5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893-2962.

6. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, A DA, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S, Document Reviewers: Osmar A. Centurion K-HKKKPJLSMSJHS, Gaurav AU, Review coordinator: Alena S. EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: Definition, characterisation, and clinical implication. *J Arrhythm* 2016;**32**:247-278.

7. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac Fibrosis in Patients With Atrial Fibrillation: Mechanisms and Clinical Implications. *J Am Coll Cardiol* 2015;**66**:943-959.

8. Kim TH, Shim CY, Park JH, Nam CM, Uhm JS, Joung B, Lee MH, Pak HN. Left ventricular diastolic dysfunction is associated with atrial remodeling and risk or presence of stroke in patients with paroxysmal atrial fibrillation. *J Cardiol* 2016;**68**:104-109.

9. Park JH, Joung B, Son NH, Shim JM, Lee MH, Hwang C, Pak HN. The electroanatomical remodelling of the left atrium is related to CHADS2/CHA2DS2VASc score and events of stroke in patients with atrial fibrillation. *Europace* 2011;**13**:1541-1549.

10. Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F, Carluccio E, Sardone MG, Porcellati C. Atrial fibrillation in hypertension: predictors and outcome. *Hypertension* 2003;**41**:218-223.

11. Lip GY, Frison L, Grind M, Invetigators S. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;**28**:752-759.

12. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049-1056.

13. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke* 1999;**30**:1223-1229.

14. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**:183-187.

15. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, Yu HT, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. Ideal Blood Pressure in Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2018;**72**:1233-1245.

16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ, National Heart L, Blood Institute Joint National Committee on Prevention DE, Treatment of High Blood P, National High Blood Pressure Education Program Coordinating C. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;**289**:2560-2572.

17. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159-2219.

18. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD, Wright JT, Jr. 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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017.

19. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, Park JY, Lee KU, Ko KS, Lee BW. Background and data configuration process of a nationwide population-based study using the korean national health insurance system. *Diabetes Metab J* 2014;**38**:395-403.

20. Lee YH, Han K, Ko SH, Ko KS, Lee KU, Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes A. Data Analytic Process of a Nationwide Population-Based Study Using National Health Information Database Established by National Health Insurance Service. *Diabetes Metab J* 2016;**40**:79-82.

21. Kim TH, Yang PS, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. CHA2DS2-VASc Score (Congestive Heart Failure, Hypertension, Age >/=75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65-74, Female) for Stroke in Asian Patients With Atrial Fibrillation: A Korean Nationwide Sample Cohort Study. *Stroke* 2017;**48**:1524-1530.

22. Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, Singer DE. Effect of Diabetes and Glycemic Control on Ischemic Stroke Risk in AF Patients: ATRIA Study. *J Am Coll Cardiol* 2016;**67**:239-247.

23. Overvad TF, Skjoth F, Lip GY, Lane DA, Albertsen IE, Rasmussen LH, Larsen TB. Duration of Diabetes Mellitus and Risk of Thromboembolism and Bleeding in Atrial Fibrillation: Nationwide Cohort Study. *Stroke* 2015;**46**:2168-2174.

24. Johansson BB. Hypertension mechanisms causing stroke. *Clin Exp Pharmacol Physiol* 1999;**26**:563-565.

25. Lee H, Kim TH, Baek YS, Uhm JS, Pak HN, Lee MH, Joung B. The Trends of Atrial Fibrillation-Related Hospital Visit and Cost, Treatment Pattern and Mortality in Korea: 10-Year Nationwide Sample Cohort Data. *Korean Circ J* 2017;**47**:56-64.

26. Baek YS, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, Lee MH, Joung B. Associations of Abdominal Obesity and New-Onset Atrial Fibrillation in the General Population. *J Am Heart Assoc* 2017;**6**.

27. Lee HY, Yang PS, Kim TH, Uhm JS, Pak HN, Lee MH, Joung B. Atrial fibrillation and the risk of myocardial infarction: a nation-wide propensity-matched study. *Sci Rep* 2017;**7**:12716.

28. Song S, Yang PS, Kim TH, Uhm JS, Pak HN, Lee MH, Joung B. Relation of Chronic Obstructive Pulmonary Disease to Cardiovascular Disease in the General Population. *Am J Cardiol* 2017;**120**:1399-1404.

**Table 1.** Patient characteristics by estimated hypertension duration at baseline

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Non-hypertensive**  **(n=41,282)** | **Hypertension** | | | | |
| **0 to 3 yrs**  **(n=82,804)** | **3 to 5 yrs**  **(n=30,859)** | **≥5 yrs**  **(n=91,514)** | **SMD**\* | **SMD**† |
| Age | 51±14 | 61±12 | 64±11 | 68±10 | 1.092 | 0.513 |
| <65 yrs | 33871 (82.0) | 46630 (56.3) | 14431 (46.8) | 31265 (34.2) |  |  |
| 65-74yrs | 5453 (13.3) | 25557 (30.9) | 5330 (35.9) | 23938 (39.6) |  |  |
| >75yrs | 1958 (4.7) | 10617 (12.8) | 5330 (17.3) | 23938 (26.2) |  |  |
| Women | 16738 (40.5) | 31260 (37.8) | 13196 (42.8) | 41831 (45.7) | 0.031 | 0.134 |
| CHA2DS2-VASc score | 0.8±1.0 | 2.5±1.6 | 3.2±1.6 | 3.8±1.8 | 1.636 | 0.622 |
| TIA/ischemic stroke Hx | 1858 (4.5) | 11446 (13.8) | 6165 (20.0) | 25785 (28.2) | 0.514 | 0.311 |
| Vascular disease | 1269 (3.1) | 10234 (12.4) | 4900 (15.9) | 21934 (24.0) | 0.503 | 0.276 |
| Previous MI | 510 (1.2) | 6034 (7.3) | 2266 (7.3) | 8724 (9.5) | 0.336 | 0.080 |
| PAD | 780 (1.9) | 5006 (6.0) | 3043 (9.9) | 15476 (16.9) | 0.391 | 0.306 |
| Heart failure | 963 (2.3) | 19082 (23.0) | 7632 (24.7) | 28052 (30.7) | 0.737 | 0.161 |
| Diabetes | 2149 (5.2) | 12400 (15.0) | 6406 (20.8) | 25627 (28.0) | 0.497 | 0.278 |
| ESRD | 1 (0.0) | 5 (0.0) | 8 (0.0) | 147 (0.2) | 0.038 | 0.051 |
| CKD | 363 (0.9) | 1756 (2.1) | 1067 (3.5) | 5965 (6.5) | 0.216 | 0.196 |
| Dyslipidemia | 13254 (32.1) | 40946 (49.4) | 19325 (62.6) | 71811 (78.5) | 0.682 | 0.557 |
| Household income |  |  |  |  | 0.034 | 0.176 |
| Upper 20% | 10558 (25.6) | 18866 (22.8) | 7312 (23.7) | 26820 (29.3) |  |  |
| Middle 40% | 16195 (39.2) | 29133 (35.2) | 11125 (36.1) | 33419 (36.5) |  |  |
| Lower 40% | 14529 (35.2) | 34805 (42.0) | 12422 (40.3) | 31275 (34.2) |  |  |
| SBP, mmHg | 121.72±15.67 | 129.03±17.89 | 130.70±17.43 | 130.47±16.74 | 0.869 | 0.057 |
| DBP, mmHg | 75.86±10.33 | 79.69±11.59 | 80.06±11.28 | 79.09±10.90 | 0.593 | 0.063 |
| Smoking |  |  |  |  | 0.185 | 0.095 |
| Current | 9558 (23.4) | 15299 (18.80) | 4647 (15.3) | 11325 (12.4) |  |  |
| Former | 6942 (17.0) | 13522 (16.6) | 4975 (16.4) | 18535 (20.4) |  |  |
| BMI | 23.2±3.0 | 24.2±3.3 | 24.5±3.3 | 24.7±3.4 | 0.408 | 0.131 |
| **≥**25 | 13323 (32.3) | 37909 (45.8) | 15270 (49.5) | 47709 (52.1) | 0.349 | 0.107 |
| **≥**30 | 1044 (2.5) | 4412 (5.3) | 2067 (6.7) | 7315 (8.0) | 0.201 | 0.091 |
| LDL cholesterol | 113.5±34.0 | 110.2±36.1 | 108.4±36.2 | 105.3±35.7 | 0.130 | 0.080 |
| eGFR | 88.2±19.8 | 81.0±19.8 | 77.7±19.8 | 72.4±20.7 | 0.653 | 0.374 |
| Medication |  |  |  |  |  |  |
| Antiplatelet agent | 1799 (4.4) | 28130 (34.0) | 14567 (47.2) | 58292 (63.7) | 1.175 | 0.542 |
| Statin | 2688 (6.5) | 12753 (15.4) | 7855 (25.5) | 38237 (41.8) | 0.609 | 0.534 |
| Beta-blocker | 1778 (4.3) | 20096 (24.3) | 11835 (38.4) | 49520 (54.1) | 0.945 | 0.548 |
| RAS blockade | 82 (0.2) | 22186 (26.8) | 13780 (44.7) | 57460 (62.8) | 1.282 | 0.657 |
| Calcium-Channel blocker | 93 (0.2) | 17394 (21.0) | 14436 (46.8) | 60588 (66.2) | 1.268 | 0.828 |
| Loop/thiazide diuretics | 733 (1.8) | 22259 (26.9) | 13899 (45.0) | 57403 (62.7) | 1.203 | 0.651 |
| K+ sparing diuretics | 271 (0.7) | 5071 (6.1) | 2062 (6.7) | 8215 (9.0) | 0.351 | 0.102 |

Values are expressed in n (%) or mean±SD. BMI = body mass index, CKD = chronic kidney disease, DBP = diastolic blood pressure, Duration of hypertension = Duration of hypertension at the time of AF diagnosis, eGFR = estimated glomerular filtration rate (ml/min/1.73m2), ESRD = end-stage renal disease, HTN = hypertension, Hx = history, LDL = low-density lipoprotein, MI = myocardial infarction, PAD = Peripheral arterial disease, RAS = renin-angiotensin system, SBP = systolic blood pressure, TIA = transient ischemic attack, Vascular disease includes previous myocardial infarction, PAD or aortic plaque. \*Standardized difference between non-hypertensive vs. hypertension. †Standardized difference between hypertension with duration ≥ 5years vs. hypertension with duration < 5 years.

**Table 2.** Duration of hypertension and hazard ratios for 1-year ischemic stroke

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Non-hypertensive** | **Hypertension Duration at AF diagnosis** | | |
|  | **0 to 3 years** | **3 to 5 years** | **≥5 years** |
| Ischemic stroke events (1-year outcome) | 1,215 | 4,887 | 2,619 | 9,033 |
| Person-Years | 36,462 | 70,099 | 24,204 | 66,275 |
| Stroke rate, 100 person-years [95% CI] | 3.33 [3.15 – 3.53] | 6.97 [6.78 – 7.17] | 10.82 [10.41 – 11.24] | 13.63 [13.35 -13.91] |
| Among all patients |  |  |  |  |
| HR (unadjusted) [95% CI] | Ref | 2.04 [1.91 – 2.17] | 2.98 [2.78 – 3.19] | 3.40 [3.18 – 3.63] |
| HR (adjusted\*) [95% CI] | Ref | 1.32 [1.24 – 1.42] | 1.50 [1.38 – 1.64] | 1.52 [1.39 – 1.65] |
| HR (age-stratified†) [95% CI] | Ref | 1.32 [1.23 – 1.41] | 1.50 [1.38 – 1.63] | 1.51 [1.39 – 1.65] |
| Among hypertensive patients |  |  |  |  |
| HR (unadjusted) [95% CI] | N/A | Ref | 1.48 [1.41 – 1.55] | 1.76 [1.70 – 1.82] |
| HR (adjusted\*) [95% CI] | N/A | Ref | 1.31 [1.25 – 1.38] | 1.40 [1.35 – 1.46] |
| HR (age-stratified†) [95% CI] | N/A | Ref | 1.33 [1.26 – 1.39] | 1.41 [1.36 – 1.47] |
| HR (unadjusted) [95% CI] | N/A | N/A | Ref | 1.19 [1.14 – 1.25] |
| HR (adjusted\*) [95% CI] | N/A | N/A | Ref | 1.07 [1.03 – 1.12] |
| HR (age-stratified†) [95% CI] | N/A | N/A | Ref | 1.06 [1.01 – 1.10] |

Duration of hypertension = Duration of hypertension at the time of AF diagnosis, HR = Hazard ratio.

\*Adjusted for CHA2DS2-VASc components (congestive heart failure, hypertension, age [continuous covariate], previous stroke, vascular disease, and sex), dyslipidemia, chronic kidney disease, body mass index, smoking status, income status, and systolic blood pressure level.

† Adjusted for CHA2DS2-VASc components (congestive heart failure, hypertension, age [continuous covariate], previous stroke, vascular disease, and sex), dyslipidemia, chronic kidney disease, body mass index, smoking status, income status, and systolic blood pressure level + additionally adjusted for age deciles (stratified cox proportional hazards model).

**Table 3.** Subgroup analyses and sensitivity analyses of the adjusted hazard ratios of 1-year ischemic stroke associated with duration of hypertension

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Adjusted Hazard Ratio [95% CI]**  **(per 1-year increase)** |  | |
| **Total population** | 1.05 [1.04 – 1.06] |  |
| **Subgroup Analyses** |  | **P for interaction** |
| Heart failure |  |  |
| Yes | 1.12 [1.10 – 1.15] | <0.001 |
| No | 1.02 [1.01 – 1.03] |
| Diabetes mellitus |  |  |
| Yes | 1.06 [1.04 – 1.08] | 0.903 |
| No | 1.04 [1.03 – 1.05] |
| Prior stroke/TIA |  |  |
| Yes | 1.04 [1.02 – 1.06] | 0.294 |
| No | 1.05 [1.03 – 1.06] |
| Chronic kidney disease |  |  |
| Yes | 1.05 [1.00 – 1.12] | 0.379 |
| No | 1.04 [1.03 – 1.05] |
| **Sensitivity Analyses** |  |  |
| excluded patients with prior stroke/TIA history | 1.06 [1.05 – 1.06] |  |
| excluded patients with baseline comorbidities such as heart failure, diabetes, vascular disease, and chronic kidney disease | 1.06 [1.05 – 1.06] |  |
| excluded patients with intracranial hemorrhage occurred during follow-up period | 1.03 [1.02 – 1.03] |  |
| included systemic embolic event as an outcome | 1.03 [1.02 – 1.03] |  |

Duration of hypertension = Duration of hypertension at the time of AF diagnosis, TIA = transient ischemic attack.

**Figure Legends**

**Figure 1.** Flowchart of Study Population enrollment and analyses.

**Figure 2.** Duration of hypertension at the time of AF diagnosis and adjusted hazard ratios for ischemic stroke in patients with atrial fibrillation. Curves represent hazard ratios adjusted for CHA2DS2-VASc components, dyslipidemia, chronic kidney disease, smoking status, body mass index, income status, and SBP level. Solid red lines are the best-fitted linear models, and blue color areas are 95% confidence intervals for the spline curves. Patients with hypertension duration under 1 year are used as reference.

**Figure 3.** Duration of hypertension at the time of AF diagnosis and adjusted hazard ratios for 1-year ischemic stroke in AF patients with different age categories. A, age < 55 years. B, age 55-64 years. C, age 65-74 years. D, age ≥ 75 years. Patients with hypertension duration under 1 year are used as reference.

**Figure 4.** Risk of ischemic stroke according to duration of hypertension in patients with different baseline SBP subgroups. A, baseline SBP < 120 mmHg. B, baseline SBP 120-139 mmHg. C, baseline SBP 140-159 mmHg. D, baseline SBP ≥160 mmHg. Duration of hypertension = duration of hypertension at the time of AF diagnosis.

**Figure 5.** Risk of ischemic stroke according to duration of hypertension in patients with atrial fibrillation in different pre-AF average SBP subgroups. A, baseline SBP < 120 mmHg. B, baseline SBP 120-139 mmHg. C, baseline SBP 140-159 mmHg. D, baseline SBP ≥160 mmHg. Duration of hypertension = duration of hypertension at the time of AF diagnosis.