

# 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population

Kim, Daehoon; Yang, Pil-Sung; Jang, Eunsun; Yu, Hee Tae; Kim, Tae-hoon; Uhm, Jae-sun; Kim, Jong-Youn; Pak, Hui-Nam; Lee, Moon-Hyoung; Joung, Boyoung; Lip, Gregory

DOI:  
[10.1016/j.ahj.2018.04.017](https://doi.org/10.1016/j.ahj.2018.04.017)

License:  
Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*  
Peer reviewed version

*Citation for published version (Harvard):*  
Kim, D, Yang, P-S, Jang, E, Yu, HT, Kim, T, Uhm, J, Kim, J-Y, Pak, H-N, Lee, M-H, Joung, B & Lip, G 2018, '10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population', *American Heart Journal*, vol. 202, pp. 20-26. <https://doi.org/10.1016/j.ahj.2018.04.017>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

Download date: 19. Jun. 2021

## Accepted Manuscript

10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population

Daehoon Kim, Pil-Sung Yang, Eunsun Jang, Hee Tae Yu, Tae-Hoon Kim, Jae-Sun Uhm, Jong-Youn Kim, Hui-Nam Pak, Moon-Hyoung Lee, Boyoung Joung, Gregory YH Lip

PII: S0002-8703(18)30140-6  
DOI: doi:[10.1016/j.ahj.2018.04.017](https://doi.org/10.1016/j.ahj.2018.04.017)  
Reference: YMHJ 5685

To appear in:

Received date: 16 January 2018  
Accepted date: 16 April 2018

Please cite this article as: Daehoon Kim, Pil-Sung Yang, Eunsun Jang, Hee Tae Yu, Tae-Hoon Kim, Jae-Sun Uhm, Jong-Youn Kim, Hui-Nam Pak, Moon-Hyoung Lee, Boyoung Joung, Gregory YH Lip , 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Ymhj(2018), doi:[10.1016/j.ahj.2018.04.017](https://doi.org/10.1016/j.ahj.2018.04.017)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Clinical investigation****10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation: nationwide health insurance data covering the entire Korean population**

Daehoon Kim, MD<sup>\*1</sup>; Pil-Sung Yang, MD<sup>\*2,1</sup>; Eunsun Jang<sup>1</sup>; Hee Tae Yu, MD<sup>1</sup>; Tae-Hoon Kim, MD<sup>1</sup>; Jae-Sun Uhm, MD<sup>1</sup>; Jong-Youn Kim, MD<sup>1</sup>; Hui-Nam Pak, MD<sup>1</sup>; Moon-Hyoung Lee, MD<sup>1</sup>; Boyoung Joung, MD<sup>†1</sup>; and Gregory YH Lip, MD<sup>†,3,4</sup>

<sup>1</sup>Division of Cardiology, Department of Internal Medicine, Yonsei University Health System, Seoul, Korea; <sup>2</sup>Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Korea; <sup>3</sup>Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, England, United Kingdom; <sup>4</sup>Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

\*These authors contributed equally to this work.

†Joint senior authors

**Running title:** Increasing burden of atrial fibrillation

**Address for correspondence:**

Boyoung Joung, MD  
50 Yonseiro, Seodaemun-gu,  
Seoul 03722, Korea

Phone: +82-2-2228-8460

Fax: +82-2-393-2041

E-mail: cby6908@yuhs.ac

Gregory YH Lip, MD  
Institute of Cardiovascular Sciences,  
University of Birmingham, Birmingham,  
England, United Kingdom

E-mail: g.y.h.lip@bham.ac.uk

**Abstract**

**Background:** Most data on the clinical epidemiology of atrial fibrillation (AF) are reported from Western populations, and data for Asians are limited. We aimed to investigate the 10-year trends of the prevalence and incidence of non-valvular AF and provide prevalence projections till 2060 in Korea. We also investigated the annual risks of adverse outcomes among patients with AF.

**Methods:** Using the Korean National Health Insurance Service database involving the entire Korean population, a total of 679,416 adults with newly diagnosed AF were identified from 2006 to 2015. The incidence and prevalence of AF and risk of adverse outcomes following AF onset were assessed.

**Results:** The prevalence of AF progressively increased by 2.10-fold from 0.73% in 2006 to 1.53% in 2015. The trend of its incidence was flat with a 10-year overall incidence of 1.77 per 1,000 person-years. The prevalence of AF is expected to reach 5.81% (2,290,591 patients with AF) in 2060. For a decade, the risk of all-cause mortality following AF declined by 30% (adjusted hazard ratio [HR]: 0.70, 95% confidence interval [CI]: 0.68–0.72), heart failure by 52% (adjusted HR: 0.48, 95% CI: 0.44–0.51), and ischemic stroke by 9% (adjusted HR: 0.91, 95% CI: 0.88–0.93).

**Conclusions:** The burden of AF among Asian patients is increasing. Although the overall risks of cardiovascular events and death following AF onset have decreased over a decade, the event rates are still high. Optimized management of any associated comorbidities should be part of the holistic management approach for patients with AF.

**Keywords:** atrial fibrillation; epidemiology; incidence; prevalence; projection; adverse outcomes

## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population.<sup>1,2</sup> The prevalence of AF has been projected to increase to 12 million individuals in the USA by the year 2050 and 17.9 million in Europe by the year 2060, with more than half of these patients aged  $\geq 80$  years, leading to a substantial public health and economic burden.<sup>3,4</sup> The age distribution of AF populations in developed countries is expected to shift in the coming years with older age groups becoming more prominent. With population aging, AF is likely to become a greater public health burden; thus, reliable prevalence and incidence figures are needed for both clinicians and policy-makers.<sup>5</sup>

AF increases the risk of mortality and morbidity resulting from stroke, congestive heart failure, and impaired quality of life, explaining its enormous socioeconomic and healthcare implications.<sup>6</sup> In recent years, important improvements have been made in pharmacological and nonpharmacological treatment of associated diseases, such as hypertension, myocardial infarction, and heart failure.<sup>7,8</sup> However, the current knowledge on the incidence, prevalence, and associated cardiovascular morbidity and mortality of AF has been predominantly derived from Western countries.<sup>9</sup>

We investigated the temporal trends of the prevalence and incidence of non-valvular AF, projected prevalence of AF to 2060, and risks of cardiovascular events and all-cause mortality using the National Health Insurance Service (NHIS) database of the entire Korean population from 2006 to 2015.

## Materials and methods

This nationwide study was based on the national health claims database established by the NHIS of Korea.<sup>10-14</sup> An insured individual should pay a national health insurance, which is proportional to the individual's income. Although the user charge exists, it is mandatory for all Koreans to join the Korean NHIS. The majority (97.1%) of the Korean population is mandatory subscribers. The remaining 3% of the population with low income is covered by the Medical Aid program. Since 2006, the information of Medical Aid beneficiaries has been incorporated into the NHIS database. Therefore, the data extracted from the NHIS database are indeed based on the entire Korean population, not causing selection bias. The following medical information is provided: patients' sociodemographic information, their use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data. Every population in the NHIS database was linked with the Korean social security numbers, and all social security numbers were deleted after constructing the cohort by providing serial numbers to prevent leakage of personal information. These databases are open to researchers whose study protocols are approved by the official review committee. This study was approved by the institutional review board of Yonsei University Health System (4-2016-0179). The need for informed consent was waived.

### *Incidence, prevalence, and projected number of non-valvular AF*

The annual incidence was defined as the rate of acquisition of a new AF diagnosis in the health claims data within a 1-year period. To qualify as an incident case, an AF diagnosis must have occurred between January 1, 2006 and December 31, 2015 (with the index date being the first date of diagnosis within this observation period). AF was diagnosed using the International Classification of Disease 10th Revision (ICD-10) codes I48 (AF and atrial flutter), I48.0 (AF),

and I48.1 (atrial flutter). We regarded the first date of obtaining the AF-related ICD-10 codes as the newly diagnosed year and excluded the first 4 years (2002 to 2005) to avoid the possibility for misdiagnosis of preexisting AF for incident AF. Moreover, the patients were considered to have AF only when AF was only a discharge diagnosis or confirmed more than twice in the outpatient department to ensure diagnostic accuracy. The diagnosis of AF has previously been validated in the NHIS database with a positive predictive value (PPV) of 94.1%.<sup>11, 14</sup> We excluded patients aged <20 years and patients with valvular heart disease (with a diagnosis of mitral stenosis [ICD-10: I05.0, I05.2, and I34.2] or prosthetic heart valves [ICD-10: Z95.2–Z95.4] and insurance claims for valve replacement or valvuloplasty).

The annual prevalence of AF was calculated by dividing the number of patients with AF alive at the end of each year by the number of the total Korean residents alive at the end of that year. Supplementary Table I shows the number and distribution of the total Korean residents aged  $\geq 20$  years. The annual incidence rates of AF in each year were calculated by dividing the number of incident cases of AF by the number of person-years at risk among all Korean residents of that year who had never been diagnosed with AF. The incidence was presented per 1,000 person-years. The incidence and prevalence rates were calculated per sex and age group (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and  $\geq 80$  years).

The projection of the prevalence of AF was also calculated using a prevalence model as previously described.<sup>3, 15</sup> The details of the prevalence model we used are described in the “Projected number of AF” section in the Supplementary Methods.

### *Definitions of comorbidities and adverse outcomes*

We obtained information on selected comorbidities from the inpatient and outpatient hospital diagnoses (all available primary and secondary diagnoses). Comorbidities were defined using the medical claims according to the ICD-10 codes and prescription medication use at the time of AF diagnosis. To ensure diagnostic accuracy, the patients were considered to have comorbidities (including heart failure, hypertension, diabetes, previous ischemic stroke/transient ischemic attack [TIA], previous intracranial bleeding, previous myocardial infarction, peripheral arterial disease [PAD], chronic kidney disease [CKD], and malignant neoplasm) when the condition was a discharge diagnosis or was confirmed more than twice in an outpatient setting, which is similar to the methods of previous studies that used the NHIS data.<sup>10-14</sup> Economic status was categorized into three groups based on the total amount of national health insurance premiums paid by the insured individual in each year, which is proportional to the individual's income: low, intermediate, and high economic status.

We followed up all patients with incidental AF and investigated the epidemiological trends of five adverse outcomes, including all-cause mortality, ischemic stroke, intracranial bleeding, heart failure admission, and myocardial infarction. The diagnostic accuracies of myocardial infarction (PPV: 86.5%), ischemic stroke (PPV: 88–95%), and intracranial bleeding (PPV: 78–92%) in the Korean NHIS have been validated previously.<sup>13, 16</sup> The definitions of comorbidities and adverse outcomes are presented in Supplementary Table II.

### ***Statistical analysis***

Data were presented as means  $\pm$  standard deviations or medians  $\pm$  interquartile ranges (IQRs) for continuous variables and proportions for categorical variables. The Cochran-Armitage



trend test was used for analyzing the temporal trends of categorical variables. The nonparametric test for trend by Jonckheere-Terpstra was used for continuous variables.

We investigated the risks of adverse outcomes in two different manners: (i) We calculated the annual risk (%/year) of adverse outcomes among the total patients with prevalent AF and non-AF population of Korea by dividing the number of the first lifetime event that occurred in each year by the total number of patients at the start of the year who had never experienced the event. Since the risks of ischemic stroke, intracranial bleeding, and myocardial infarction might be associated with the use of antithrombotic therapies, we analyzed these risks among the patients who did not receive antithrombotic therapies within 90 days after enrollment. Adverse outcomes among the non-AF Korean population were evaluated using an age- and sex-matched cohort derived from the Korean NHIS-National Sample Cohort database. The details of the non-AF cohort are presented in the “Non-AF cohort from the Korean National Health Insurance Service-National Sample Cohort database” section of the Supplementary Methods. (ii) We also investigated the association between the calendar years of AF diagnosis and adverse outcomes on the 2-year follow-up after AF diagnosis using Cox-proportional hazard regression analysis. We estimated the hazard ratios (HRs) of 7 calendar years of AF diagnosis (2007-2013) with 2006 as the reference calendar year. The HRs were adjusted for age, sex, economic status, and comorbidities at the time of diagnosis, including heart failure, hypertension, diabetes, previous ischemic stroke/TIA, previous intracranial bleeding, previous myocardial infarction, PAD, CKD, and malignant neoplasm.

All tests were two-tailed, with P values of  $<0.05$  considered significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), R version 3.4.1, and SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

***Sources of funding***

This work 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) and grants from the Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (HI16C0058, HI15C1200). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript and its final contents.

## Results

### *Patient characteristics*

During a total of 384,266,047 person-years of follow-up, we identified 679,416 patients in the general population with first-time AF diagnosed between 2006 and 2015. The characteristics of the patients with newly diagnosed AF in Korea between 2006 and 2015 are presented in Table I. The AF diagnoses were almost equally distributed between the men and women and stable over time. The proportion of the men increased modestly from 51.7% in 2006 to 54.2% in 2015 (P value for trend <0.001). The median age of the patients with AF increased from 65 (IQR: 53–74) years in 2006 to 71 (IQR: 59–79) years in 2015 (P value for trend <0.001). The proportion of the elderly aged 70–79 and  $\geq 80$  years gradually increased from 25.6% and 12.0% in 2006 to 29.0% and 23.2% in 2015 (both P values for trend <0.001), respectively. The proportion of the patients with intermediate and high economic status increased significantly, while the proportion of the patients with low economic status decreased from 49.1% in 2006 to 30.0% in 2015 (all P values for trend <0.001).

The comorbidity burden increased over time. The most prevalent comorbidities during the 10-year period were hypertension (71.1%), heart failure (24.9%), malignant neoplasm (23.0%), diabetes (22.7%), and ischemic stroke (19.6%).

**Table I. Characteristics of the patients with newly diagnosed AF in Korea between 2006 and 2015**

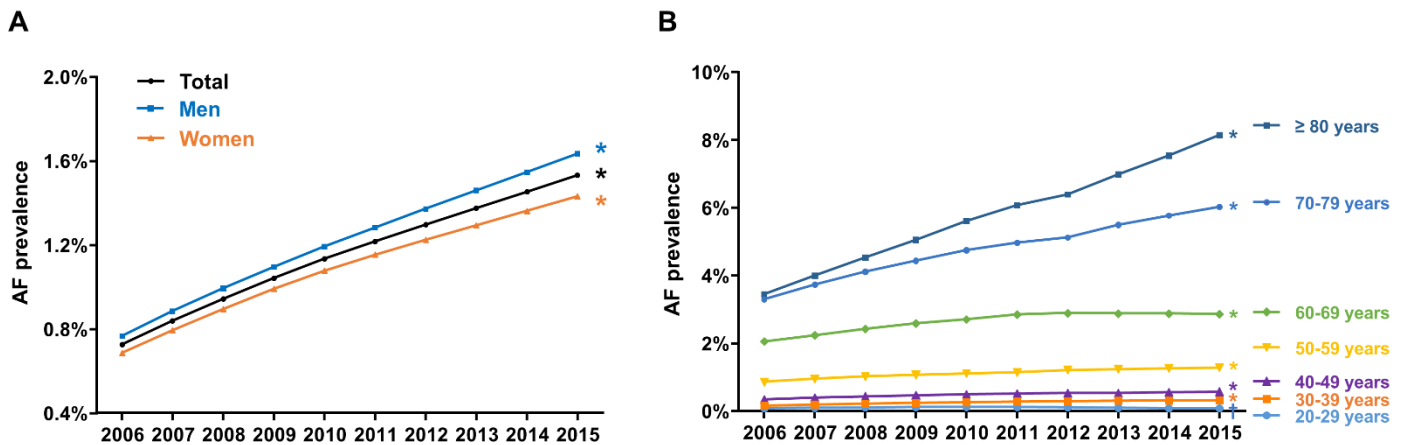
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Overall	P value for trend
Newly diagnosed AF, n	66,903	66,986	65,829	66,100	67,071	66,743	68,461	69,642	69,961	71,720	679,416	
Age, median (IQR)	65 (53–74)	65 (53–74)	66 (54–75)	67 (54–75)	67 (55–75)	68 (55–76)	68 (56–76)	70 (58–78)	70 (58–78)	71 (59–79)	68 (56–76)	<0.001
20–29 years, %	2.7	2.8	2.5	2.4	2.2	2.0	1.8	1.4	1.5	1.7	2.1	<0.001
30–39 years, %	5.1	5.2	5.0	4.7	4.5	4.3	3.8	3.3	3.2	3.2	4.2	<0.001
40–49 years, %	11.2	11.2	10.5	10.2	9.7	8.9	8.4	7.1	7.0	7.0	9.1	<0.001
50–59 years, %	16.9	17.1	17.1	16.5	16.6	17.1	17.4	16.1	15.8	14.9	16.5	<0.001
60–69 years, %	26.5	25.6	25.3	24.9	24.1	23.4	22.9	21.0	20.8	21.1	23.5	<0.001
70–79 years, %	25.6	25.9	26.7	27.4	27.7	28.5	29.1	30.6	30.0	29.0	28.1	<0.001
≥80 years, %	12.0	12.2	13.0	13.9	15.1	15.8	16.7	20.4	21.8	23.2	16.5	<0.001
Sex, %												
Male	51.7	52.4	52.3	51.9	52.7	53.3	53.3	54.1	54.1	54.2	53.0	<0.001
Female	48.3	47.6	47.7	48.1	47.3	46.7	46.7	45.9	45.9	45.8	47.0	<0.001
Economic status, %												
Low	49.1	44.3	40.5	38.1	41.8	38.8	36.6	30.5	29.7	30.0	37.8	<0.001

Intermediate	20.6	38.2	23.9	24.1	23.9	23.9	23.5	24.0	25.0	25.0	25.2	<0.001
High	30.3	17.5	35.6	37.8	34.3	37.3	40.0	45.5	45.3	45.0	37.0	<0.001
Comorbidities, %												
Heart failure	22.2	22.8	23.4	23.7	24.0	24.5	25.5	26.5	27.7	28.2	24.9	<0.001
Hypertension	64.1	66.5	68.4	70.0	71.7	71.8	73.4	75.1	74.9	74.2	71.1	<0.001
Diabetes	18.5	19.6	20.5	21.6	22.3	22.9	23.8	25.3	26.0	26.2	22.7	<0.001
Ischemic stroke	14.2	16.0	17.1	19.0	20.2	20.1	21.2	22.6	23.0	22.2	19.6	<0.001
Intracranial bleeding	1.8	2.0	2.0	2.2	2.6	2.5	2.6	2.7	2.8	2.9	2.4	<0.001
MI	7.3	7.7	8.2	8.5	8.1	8.0	8.3	8.5	8.8	9.1	8.3	<0.001
PAD	5.3	6.4	7.8	10.2	11.4	12.1	13.2	14.5	15.0	15.5	11.2	<0.001
CKD	3.8	4.4	4.8	5.3	5.6	5.9	6.9	7.4	8.1	8.4	6.1	<0.001
Malignant neoplasm	15.9	17.9	19.6	21.6	22.8	24.2	25.5	25.8	27.2	28.3	23.0	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score,	2.74	2.84	2.95	3.08	3.16	3.18	3.29	3.54	3.59	3.60	3.20	<0.001
mean (SD)	(1.92)	(2.00)	(2.04)	(2.10)	(2.13)	(2.16)	(2.18)	(2.05)	(2.07)	(2.10)	(2.10)	
HAS-BLED score,	2.07	2.19	2.30	2.42	2.50	2.54	2.62	2.72	2.75	2.75	2.49	<0.001
mean (SD)	(1.38)	(1.43)	(1.45)	(1.47)	(1.48)	(1.49)	(1.50)	(1.50)	(1.52)	(1.54)	(1.59)	

AF, atrial fibrillation; CKD, chronic kidney disease; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation.

**Prevalence, incidence, and projected number of AF**

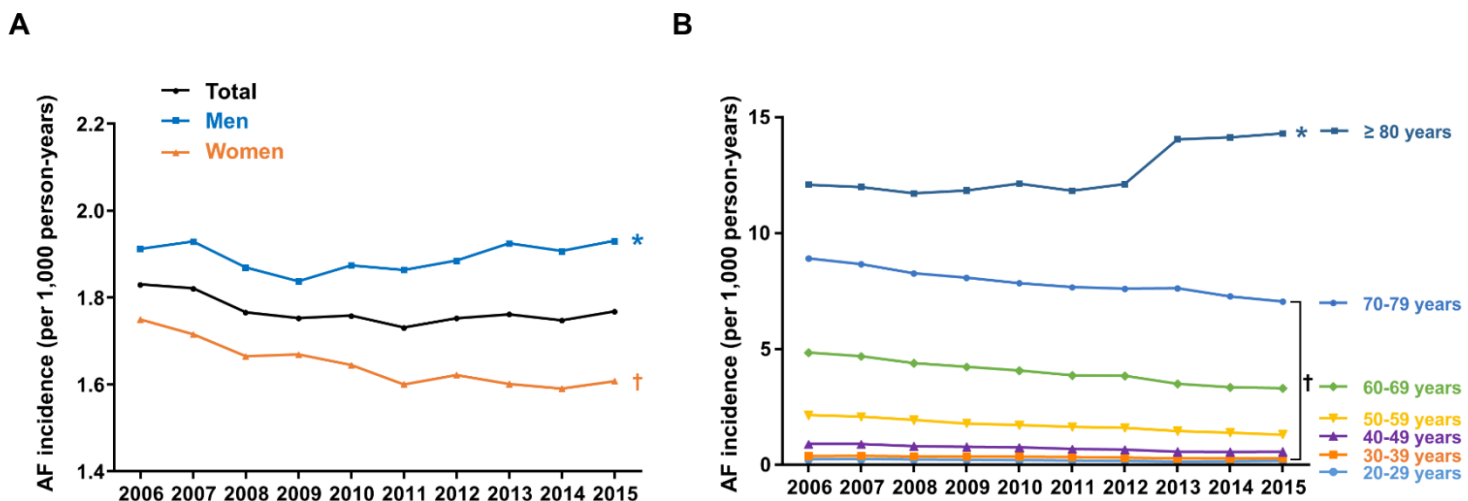
Figure 1 shows the temporal trends of the prevalence of AF in Korea. The prevalence progressively increased by 2.10-fold from 0.73% in 2006 to 1.53% in 2015 (P value for trend <0.001). The prevalence was significantly greater in the men than in the women for all years (P <0.001) (Figure 1A). Across all age groups, the prevalence consistently increased over the study period, except for the prevalence among those aged 20–29 years, which decreased significantly (all P values for trend <0.001) (Figure 1B). The prevalence of AF increased with older age, ranging from 0.09% among those aged 20–29 years to 8.15% among those aged  $\geq 80$  years in 2015 (P value for trend <0.001). The annual prevalence of AF between 2006 and 2015 stratified by sex and age is presented in Supplementary Table III.



**Figure 1. Annual prevalence of AF between 2006 and 2015 stratified according to sex (A) and age (B)**

\*P value for increasing trends <0.001. †P value for decreasing trends <0.001. AF, atrial fibrillation.

Figure 2 shows the incidence of AF from 2006 to 2015. The annual trend of AF incidence was almost flat with a 10-year overall incidence of 1.77 per 1,000 person-years. The 10-year overall incidence in the men was 1.89 per 1,000 person-years, which was 1.16 times higher than 1.65 per 1,000 person-years in the women ( $P < 0.001$ ); the tendency was consistent over the study period (Figure 2A). The annual AF incidence in the subjects aged  $\geq 80$  years significantly increased from 12.1 in 2006 to 14.3 per 1,000 person-years in 2015 ( $P$  value for trend  $< 0.001$ ), while the incidence in all other age groups decreased (all  $P$  values for trend  $< 0.001$ ) (Figure 2B and Supplementary Table IV).

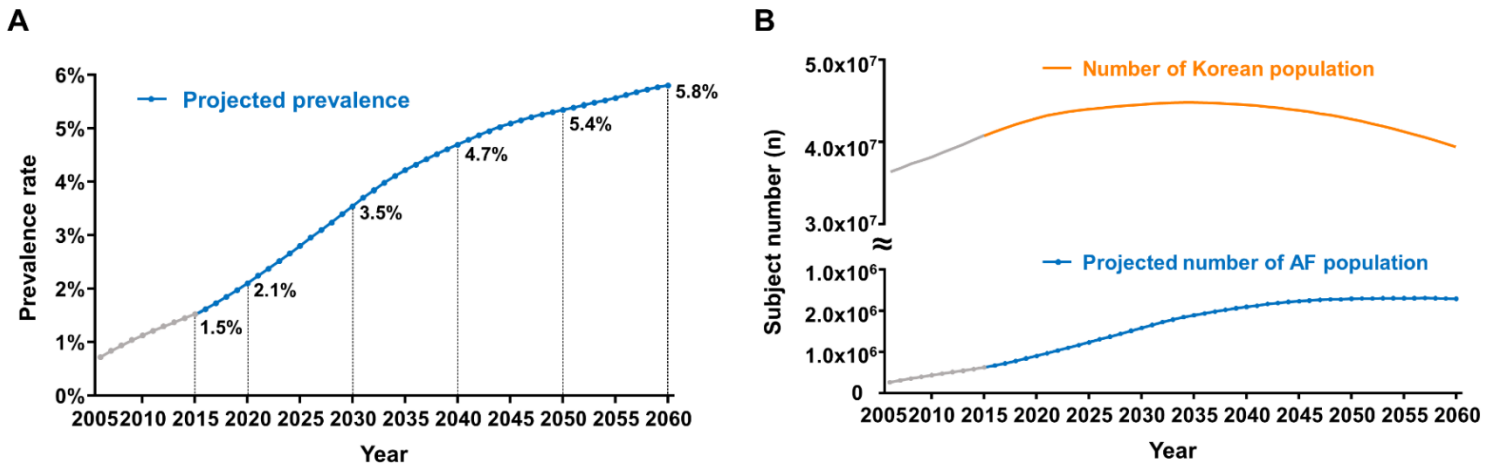


**Figure 2. Annual incidence of AF between 2006 and 2015 stratified according to sex (A) and age (B)**

\*P value for increasing trends  $< 0.001$ . †P value for decreasing trends  $< 0.001$ . AF, atrial fibrillation.

Using the prevalence model previously described and assuming that the incidence of AF and mortality remained constant beyond 2015, the projected number of adults with AF will be

2,290,538 (prevalence rate: 5.35%) in 2050 and 2,290,591 (prevalence rate: 5.81%) in 2060 (Figure 3).



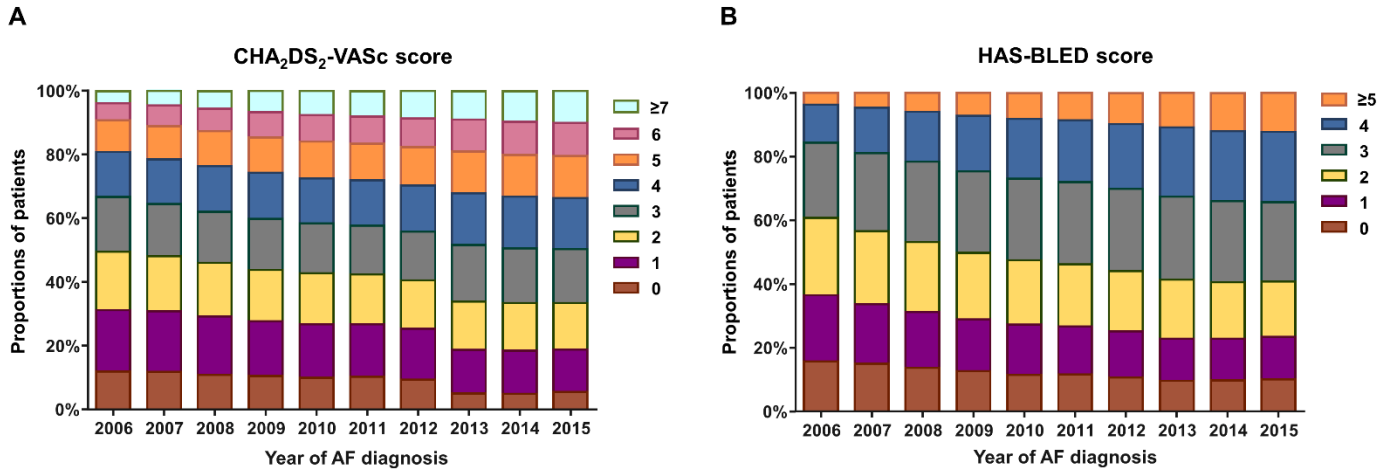
**Figure 3. Projected prevalence rate (A) and number (B) of AF**

AF, atrial fibrillation.

#### *Trends of the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores*

The distributions according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores among the patients with incident AF are presented in Figure 4. The proportion of the patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of  $\geq 2$  increased from 68.8% to 81.2% from 2006 to 2015 (P value for trend  $< 0.001$ ). The proportion of the patients with a high bleeding risk according to the HAS-BLED score of  $\geq 3$  increased from 39.3% in 2006 to 59.1% in 2015 (P value for trend  $< 0.001$ ).



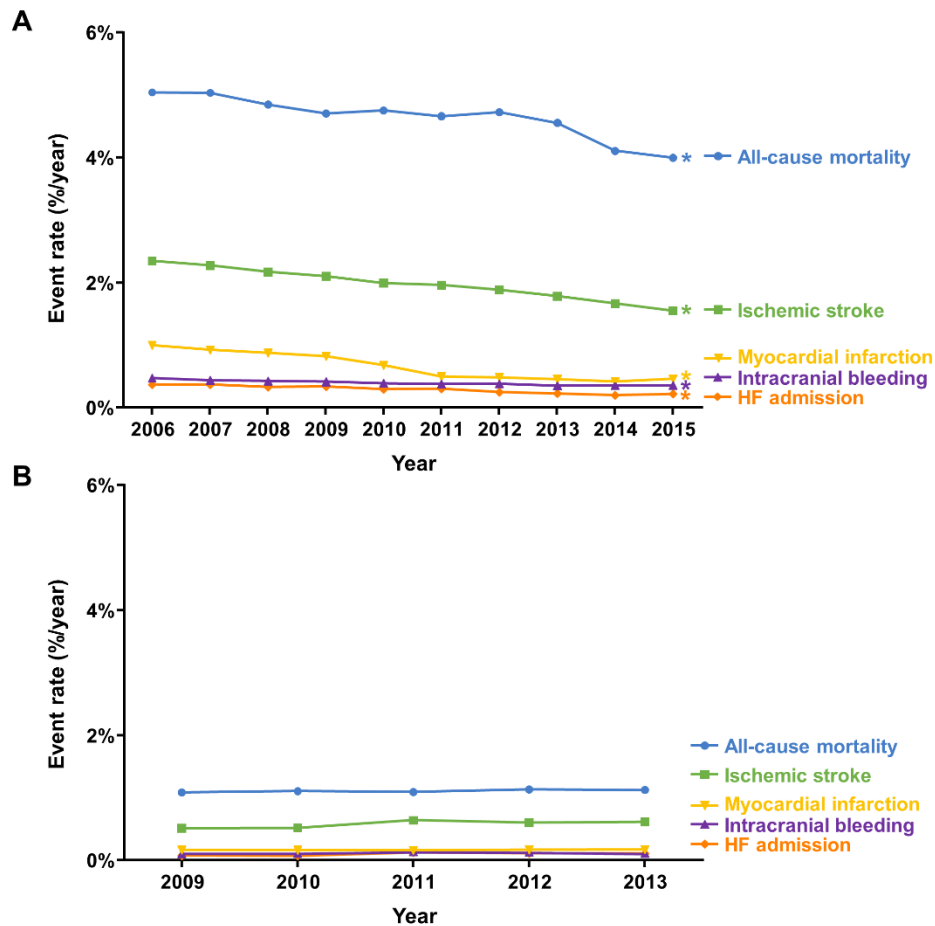


**Figure 4. Temporal trends of the distribution of the patients with newly diagnosed AF according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores between 2006 and 2015**

AF, atrial fibrillation.

#### *Trends of the adverse outcomes among the patients with AF*

The annual trends of the adverse event rates among the patients with prevalent AF and non-AF Korean population are presented in Figure 5. Among the patients with prevalent AF, the annual event rates for all-cause mortality, ischemic stroke, intracranial bleeding, heart failure admission, and myocardial infarction declined for a decade (all P values for trend <0.001). However, these did not change significantly among the non-AF Korean population.

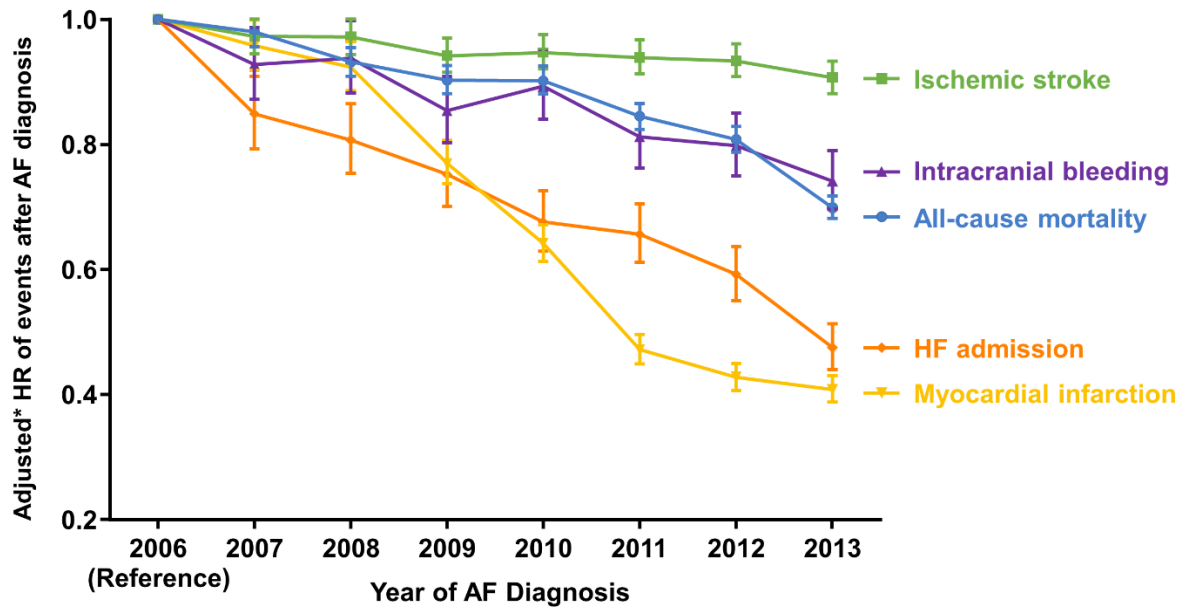


**Figure 5. Temporal trends of the 1-year adverse event rates of the (A) patients with prevalent AF and (B) non-AF Korean population in each year**

\*P value for trends <0.001. The 1-year adverse event rates (%/year) were calculated by dividing the number of the first lifetime event that occurred in each year by the total number of patients at the start of the year who had not experienced that event before. AF, atrial fibrillation; HF, heart failure.

The temporal trends of the 2-year risks of adverse outcomes following AF diagnosis are presented in Figure 6. The adjusted risk of the patients diagnosed with AF in 2013 for all-cause mortality declined by 30% (adjusted HR: 0.70, 95% confidence interval [CI]: 0.68–0.72), heart

failure by 52% (adjusted HR: 0.48, 95% CI: 0.44–0.51), myocardial infarction by 59% (adjusted HR: 0.41, 95% CI: 0.39–0.43), ischemic stroke by 9% (adjusted HR: 0.91, 95% CI: 0.88–0.93), and intracranial bleeding by 26% (adjusted HR: 0.74, 95% CI: 0.70–0.79), compared with those of the patients diagnosed in 2006 (Figure 6 and Supplementary Table V).



**Figure 6. Temporal trends of the adjusted HRs of the adverse outcomes in the 2-year follow-up after AF diagnosis**

The HR was adjusted for age, sex, economic status, and comorbidities. AF, atrial fibrillation; HF, heart failure; HR, hazard ratio.

## Discussion

To the best of our knowledge, the current study used the largest nationwide cohort consisting of the entire Korean population to estimate the current and future non-valvular AF incidence and prevalence. Our principal findings are as follows: (i) The prevalence of AF progressively increased by 2.10-fold from 0.73% in 2006 to 1.53% in 2015; (ii) the trend of annual AF incidence was flat with a 10-year overall incidence of 1.77 per 1,000 person-years; (iii) the prevalence of AF was estimated to be 5.81% in 2060; and (iv) the risks of all-cause mortality, ischemic stroke, intracranial bleeding, heart failure, and myocardial infarction following onset of AF decreased markedly over a decade.

### *Prevalence, incidence, and projected number of AF*

Over the course of 10 years of observation, we observed an increasing prevalence and a flat incidence of AF. The increase in the prevalence is in line with the findings for most Western populations.<sup>4, 17-19</sup> Across all age groups and both sexes, the prevalence consistently increased over the study period with higher absolute numbers in the older patients and men. The prevalence of AF in Korea was similar to the recently reported AF prevalence rates from 1.1% to 1.6% in other Asian countries (1.07% in Taiwan,<sup>17</sup> 1.5% in Singapore,<sup>20</sup> and 1.6% in Japan<sup>21</sup>). The prevalence of AF is generally lower in Asia than in Western countries (i.e., Caucasians).<sup>22, 23</sup> Although the precise mechanisms behind the differences in AF epidemiology between Asians and Caucasians remain unclear, part of the global variation may be attributable to the better surveillance in developed countries, and the prevalence of AF in some Asian countries is probably underestimated.<sup>22, 24</sup> Furthermore, the longer life expectancy and more prevalent

cardiovascular risk factors and diseases, including smoking, obesity, hypertension, ischemic heart diseases, and diabetes, in developed Western countries may play important roles.<sup>24</sup>

Most prior data on AF incidence rates were reported from studies performed in Europe and North America. The reported AF incidence rate ranges from 3.3 to 9.9 per 1,000 person-years among studies conducted in Europe<sup>23, 25, 26</sup> and from 3.3 to 19.2 per 1,000 person-years among predominantly USA-based cohort studies.<sup>3, 19, 27</sup> The 10-year overall incidence of AF in the present study was 1.77 per 1,000 person-years, which is lower than that in Europe and the USA. However, our AF incidence rate is comparable to those described in a Taiwanese nationwide cohort study (i.e., 1.51 per 1,000 person-years).<sup>17</sup> Consistent with our findings, the annual trend of AF incidence was stable in Taiwan.

Similar to the growing burden of AF worldwide,<sup>22</sup> the AF prevalence and the absolute number of patients with AF would continuously increase over the coming decades in Korea based on our projected estimations. Indeed, the AF prevalence in Korea was estimated to be 5.35% in 2050, which is higher than the projected AF prevalence of 4.01% in Taiwan.<sup>17</sup>

### ***Risks of adverse outcomes***

Over the last 5 decades, the AF-associated mortality decreased by 25% in the Framingham heart study.<sup>19</sup> In Korea, we observed a 20% reduction in the mortality rate over a decade from 5.0% per year in 2006 to 4.0% per year in 2015. The improved survival after AF onset may arise from (1) earlier detection (lead time) owing to heightened awareness, (2) changed diagnostic criteria (as described above), (3) enhanced surveillance of patients with AF, (4) advances in the guideline-recommended treatments for AF, including oral anticoagulation to reduce risks of embolization, and (5) more aggressive treatment of complications and

comorbidities, such as hypertension, ischemic heart disease, heart failure, and hypercholesterolemia.<sup>18</sup>

Given the high mortality associated with heart failure and stroke,<sup>28, 29</sup> the 52% reduction in heart failure subsequent to AF observed over the study period and the 9% reduction in the risk of ischemic stroke were likely to have contributed substantially to the improved survival.

Although our results showing a declining associated risk for heart failure and stroke following AF are in line with those for other Western populations,<sup>18</sup> the 1-year rates of heart failure and stroke were 0.2% and 1.8% per year, respectively, which are still higher than 0.1% and 0.6% per year of the age- and sex-matched non-AF population in 2013.

### ***Limitations***

The present study has several limitations given the nature of the nationwide registry dataset we used. Such studies using administrative databases might be susceptible to errors from coding inaccuracies. To minimize this problem, we examined the nationwide cohort and applied the definition already validated in previous studies that used the Korean NHIS sample cohort.<sup>11, 13, 14, 16</sup> Since we defined AF cases only with ICD-10 codes, it is possible that either paroxysmal or asymptomatic AF cases, which were not ascertained by these codes, were not recorded. Also, we could not analyse paroxysmal, persistent, and permanent AF subgroups separately. Patients younger than 20 years were excluded from the study population. This approach can omit some patients with AF. However, the prevalence among children and adolescents could be underestimated owing to the lack of symptoms, fewer visits to medical institutions, and lack of routine ECG check-up. Therefore, most previous studies have included only adult populations.<sup>17, 21, 23</sup> Although it would be relevant to stratify all adverse outcomes according to antithrombotic

therapies, we provided the risks of ischemic stroke, intracranial bleeding, and myocardial infarction, which could be altered by antithrombotic therapies, only among the patients who did not receive antithrombotic therapies. By investigating the risk of first lifetime events which were not affected by antithrombotic therapies, we attempted to understand the disease course after new-onset AF more clearly. Despite these limitations, this study evaluated longitudinal data from the entire Korean adult population. Therefore, our findings may reflect the “real-world” AF burden on a nationwide scale.

**Conclusion**

The burden of AF among Asian patients is increasing. Although the overall risks of death, ischemic stroke, intracranial bleeding, heart failure, and myocardial infarction following onset of AF have decreased over a decade, the absolute event rates are still high. Optimized management of any associated comorbidities should be part of the holistic management approach for patients with AF.

**Disclosures**

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

The other authors have no disclosures to make.

**Acknowledgements**

None.



**References**

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98(10):946-52.
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 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(23):e199-267.
3. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114(2):119-25.
4. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *European heart journal* 2013;34(35):2746-51.
5. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *The American journal of cardiology* 1998;82(8A):2N-9N.
6. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *The American journal of medicine* 2002;113(5):359-64.
7. Van Gelder IC, Haegeli LM, Brandes A, Heidbuchel H, Aliot E, Kautzner J, et al. Rationale and current perspective for early rhythm control therapy in atrial fibrillation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the*

- working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2011;13(11):1517-25.
8. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, et al. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2013;15(11):1540-56.
  9. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012;142(6):1489-1498.
  10. Lee H, Kim TH, Baek YS, Uhm JS, Pak HN, Lee MH, et al. The Trends of Atrial Fibrillation-Related Hospital Visit and Cost, Treatment Pattern and Mortality in Korea: 10-Year Nationwide Sample Cohort Data. *Korean circulation journal* 2017;47(1):56-64.
  11. Lee SS, Ae Kong K, Kim D, Lim YM, Yang PS, Yi JE, 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.
  12. Baek YS, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, et al. Associations of Abdominal Obesity and New-Onset Atrial Fibrillation in the General Population. *Journal of the American Heart Association* 2017;6(6).

13. Lee HY, Yang PS, Kim TH, Uhm JS, Pak HN, Lee MH, et al. Atrial fibrillation and the risk of myocardial infarction: a nation-wide propensity-matched study. *Scientific reports* 2017;7(1):12716.
14. Kim TH, Yang PS, Kim D, Yu HT, Uhm JS, Kim JY, et al. CHA2DS2-VASc Score for Identifying Truly Low-Risk Atrial Fibrillation for Stroke: A Korean Nationwide Cohort Study. *Stroke* 2017;48(11):2984-2990.
15. Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. *Journal of the American Heart Association* 2017;6(5).
16. Park TH, Choi JC. Validation of Stroke and Thrombolytic Therapy in Korean National Health Insurance Claim Data. *Journal of clinical neurology (Seoul, Korea)* 2016;12(1):42-8.
17. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, et al. Lifetime Risks, Projected Numbers, and Adverse Outcomes in Asian Patients With Atrial Fibrillation: A Report From the Taiwan Nationwide AF Cohort Study. *Chest* 2017.
18. Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Nielsen JC, Sorensen HT. 30-year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. *International journal of cardiology* 2016;225:30-36.
19. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;386(9989):154-62.

20. Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. *Journal of electrocardiology* 2008;41(2):94-8.
21. Iguchi Y, Kimura K, Aoki J, Kobayashi K, Terasawa Y, Sakai K, et al. Prevalence of atrial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: analysis of 41,436 non-employee residents in Kurashiki-city. *Circulation journal : official journal of the Japanese Circulation Society* 2008;72(6):909-13.
22. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129(8):837-47.
23. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *European heart journal* 2006;27(8):949-53.
24. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nature reviews Cardiology* 2014;11(11):639-54.
25. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, et al. Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality: A Community-Based Study From the Netherlands. *Journal of the American College of Cardiology* 2015;66(9):1000-7.
26. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working*

- groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2013;15(4):486-93.
27. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;96(7):2455-61.
  28. Schmidt M, Jacobsen JB, Johnsen SP, Botker HE, Sorensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. *Neurology* 2014;82(4):340-50.
  29. Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Sorensen HT. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of comorbidity: a Danish nationwide cohort study. *European journal of heart failure* 2016;18(5):490-9.