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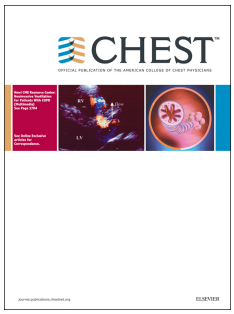

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Lifetime Risks, Projected Numbers and Adverse Outcomes in Asian Patients with Atrial Fibrillation: A Report from the Taiwan Nationwide AF Cohort Study

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Abstract

Background: Most data on the clinical epidemiology of atrial fibrillation (AF) comes from Western populations, and data for Asians are limited. We investigated the lifetime risk and projected number of AF among Asians. The annual risks of adverse events amongst AF patients, time trends and the risks compared to non-AF patients were analyzed.

Methods: From year 2000 to 2011, 289,559 patients aged ≥ 20 years experienced new-onset AF in Taiwan. The incidence, prevalence and lifetime risk of AF were calculated. The risk of adverse events amongst AF patients were analyzed and compared to that of age- and gender-matched patients without AF.

Results: The incidence of AF in year 2011 was 1.51 per 1000 person-years, with a lifetime risk of AF being appropriately 1 in 7 for subjects aged >20 years. The prevalence of AF is estimated to be 4.01% in 2050.

Compared to patients without AF, AF was associated with an increased risk of mortality (adjusted hazard ratio 2.61), heart failure (3.31), ischemic stroke (3.34), dementia (1.56), sudden cardiac death (1.83), and myocardial infarction (1.62); all p value <0.01. The risks of ischemic stroke, heart failure and mortality were especially higher compared to non-AF patients within the initial period (approx. 6 months) after AF was first diagnosed.

Conclusions: The burden of AF amongst Asian patients is increasing, with a lifetime risk of AF being appropriately 1 in 7. Optimized management of any associated comorbidities should be part of the holistic management approach for AF.

Key words: atrial fibrillation, incidence, prevalence, lifetime risk, adverse events

Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia, and its prevalence is projected to rise continuously over the next few decades due to an ageing population.[1] The lifetime risks for development of AF have been quoted as 1 in 4 for men and women 40 years of age and older based on the data of Framingham Heart Study.[2] In the Rotterdam study, the lifetime risk of developing AF at the age of 55 years was 23.8% in men and 22.2% in women.[3] In contrast to such extensive data in the white population,[4] time trends in the incidence, prevalence and lifetime risks of AF amongst Asians are limited.

AF has large impact on a person's health. Historical studies have shown that AF is associated with an increased risk of ischemic stroke, mortality and heart failure.[5-7] More recently, AF has been reported to be an important risk factor for dementia, myocardial infarction and sudden cardiac death.[8-11] Again, most of the clinical epidemiology of AF has been based on studies that mainly enrolled Caucasian population in America and Europe, and the risk of adverse events of Asian AF patients has not been well studied.

We investigated the incidence, prevalence, lifetime risk and projected number of AF among Asians. Second, we investigated the annual risks of adverse events amongst AF patients, time trends and the risks compared to non-AF patients.

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Methods

Database

This study used the "National Health Insurance Research Database (NHIRD)" released by the Taiwan National Health Research Institutes (NHRI). The National Health Insurance (NHI) system is a mandatory universal health insurance program which has been launched on March 1, 1995 that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan's population from January 1, 1996 to December 31, 2011. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the NHI database and can be followed continuously. The details about the Taiwan NHIRD could be found at the website of Taiwan NHRI (http://nhird.nhri.org.tw/en/Data_Files.html).

Study population

From January 1, 2000 to December 31, 2011, a total of 289,559 patients aged ≥ 20 years have experienced new-onset AF. The AF was assumed to be new-onset if no diagnosis of AF could be traced within the NHIRD from January 1, 1996 to the index date. The detailed health care data of each AF patients were available to December 31, 2011 unless mortality occurred earlier. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31) registered by the physicians responsible for the treatments of patients. To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed for at least 2 times in the outpatient department. We defined the date of discharge or the date of the second

documented AF in the outpatient department as the index date. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[12,13] Among the AF cohort, 158,283 patients (54.7%) were diagnosed using the discharge diagnosis. For patients who were diagnosed in the outpatient department (n = 131,276), the median durations between these 2 outpatient visits were 16 days (interquartile range = 7-56 days). For each AF patients, an age (same age in years)- and gender-matched subject without AF were identified from the NHIRD at the same index date, and the risk of adverse events were compared between AF and non-AF subjects. Patients were defined as non-AF patients if no any diagnosis of AF could be traced within the NHIRD.

Incidence, prevalence and projected number of AF

Crude incidence rates for AF of each year were calculated by dividing the number of incident cases of AF by the number of person-years accumulated by whole Taiwanese residents within 1 year. The person-years of follow up of each year are shown in Supplemental Table 1. The prevalence of AF was calculated by dividing the number of AF patients alive at the end of each year by the number of Taiwanese residents alive at the end of each year. The incidence and prevalence rates of AF for males and females for 10-year age strata were analyzed based on the incidence and prevalence rates in year 2011. For the calculation of lifetime risk, the method proposed by Sasieni et al. was used.[14] The incidence of AF among patients with death free for each age attained during the 12-year period was calculated. Lifetime risk estimates reflect the sum of age-specific incidences from study entry to age at last observation.

The formula used to calculate the projected prevalence of AF and its detailed descriptions are similar to the study by Lane et al.[15] The projection of the prevalence of

AF, p_{ij} , at age level *i* in year *j* was calculated iteratively based on age level incidence r_i and mortality M_i as

$$p_{ij} = \frac{\left(p_{i-1,j-1} + \left(1 - p_{i-1,j-1}\right) * r_i * (1+q)^j\right) * \left(1 - (1 - M_i)^{RR_{AF}}\right)}{1 - M_i}$$

with the overall relative mortality of AF patients, RR_{AF}, assumed to be constant across all ages. An annual constant increase in incidence may be given by q>0, also implying equal relative increase across age groups. Incidence of AF was based on the incidence rate of AF in Taiwan in year 2011 stratified for 5 age groups (20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and ≥80 years), whereas mortality rates were extracted from the Taiwan population statistics provided by the Department of Statistics, Taiwan Ministry of the Interior (TMI) in 2011. An excess mortality for AF compared to non-AF patients of HR = 2.61, that is, RR_{AF}=2.61 according to the results of the present study. Prevalence in 2011 was estimated directly from the AF cohort and used as a basis for the projection of prevalence from 2012 to 2050 on the assumption of a constant incidence (q=0). Using TMI projections of the Taiwan population size, $N_{TW,ij}$ at age group *i* in year *j*, the expected number of AF patients at year *j* was obtained as $N_{AF,j} = \sum_i p_{ij} * N_{TW,ij}$ and the overall prevalence $p_j = N_{AF,j} / \sum_i N_{TW,ij}$.

Definitions and risks of adverse events

In the present study, we investigated six kinds of adverse events, including mortality, ischemic stroke (433.x, 434.x, 436), heart failure (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x), dementia (290.0-290.4, 331.0), sudden cardiac death (427.5, 798.1, 798.2) and myocardial infarction (410.xx). The diagnostic accuracies of heart failure, myocardial infarction and ischemic stroke in Taiwan NHIRD have been validated before.[16-18] We investigated the risk of first-time rather than recurrent events after incident

AF and aimed to provide a picture about the disease course, namely the subsequent risks of important adverse events after new-onset AF. Since the risks of ischemic stroke and myocardial infarction could be significantly reduced with the use of antithrombotic therapies, we analyzed these risks among patients who did not receive antithrombotic therapies within 90 days after the index date. Incidence rate (per 100 person-years) of adverse events was calculated from dividing the number of event by person-time at risk, and the data were presented as the annual risk (%/year).

The risk of ischemic stroke was analyzed among AF and compared to that of non-AF patients without history of ischemic stroke who did not receive antithrombotic therapies (n = 143,684 in each groups). The risk of myocardial infarction was analyzed among AF and compared to that of non-AF patients without history of myocardial infarction who did not receive antithrombotic therapies (n = 135,065 in each groups). The risk of heart failure, dementia and sudden cardiac death were analyzed among AF and compared to that of non-AF patients without history of these events, with a patient number of 166,740, 268,679 and 288,180, respectively in each groups.

Statistical analysis

Data are presented as the mean value and standard deviation for continuous variables and proportions for categorical variables. The differences between normally distributed continuous values were assessed using an unpaired 2-tailed t test or one-way analysis of variance (ANOVA) for the comparisons of 3 groups. The differences between nominal variables were compared by Chi-square test. The cumulative incidence curves of adverse events were plotted using the Aalen–Johansen estimator with mortality being as the competing risk. The risk of adverse events for AF and non-AF patients were compared using Cox regression analyses which adjusted for age, gender and comorbidities, including

hypertension, diabetes mellitus, heart failure, vascular diseases, and previous history ischemic stroke/transient ischemic attack. We also investigated the hazard ratios (HRs) of mortality, heart failure and ischemic stroke of AF compared to non-AF patients in different timing periods ("one-month interval within 2 years" and "more than 2 years") after the index date. Data were analyzed using the SPSS PASW statistical software (IBM corporation, Armonk, NY, USA), and all statistical significances were set at a $p < 0.05$.

The present study was approved by the Institutional Review Board (IRB) at Taipei Veterans General Hospital (2016-03-002AC and 2017-07-003BC), Taipei, Taiwan and the informed consent of study subject was waived.

Results

The mean age of the 289,559 AF patients was 71.5 ± 13.3 years, and 55.3% were men. Mean $CHADS_2$ and CHA_2DS_2-VASc scores of overall AF cohort were 2.69 and 4.14, respectively; and hypertension was the most prevalent comorbidity, noted in 74.1% of patients. Table 1 presents the baseline characteristics of the AF cohort overall and by time period (200–2003, 2004–2007, and 2008–2011). There was clear evidence of an aging AF population, with the proportion of over 80-year-olds increasing from 25.7% in 2000–2003 to 33.5% in 2008–2011. Also, the prevalences of important comorbidities at the time of AF diagnosis increased. Owing to the increase in age and comorbidities, the $CHADS_2$ and CHA_2DS_2-VASc scores of incident AF patients diagnosed in each year showed a trend to become higher with successive year (Figure 1).

Incidence, prevalence, lifetime risk and projected number of AF

Figure 2A shows the incidence rate of AF from year 2000 to 2011. The incidence of AF in year 2011 was 1.51 per 1000 person-years (Figure 2A), with a stepwise increase with age (Figure 2B). The prevalence rate of AF increased from 0.46% to 1.07% over the 12 years, with a 2.33-fold increase (Figure 3A). Compared to subjects aged 50-59 years, subjects aged 60-69 years had a 2.8-fold higher in AF (2.5% versus 0.9%), whereas subjected aged 70-79 years had a nearly six-fold higher in AF (5.1% versus 0.9%) (Figure 3B). The projected prevalence rate was estimated to be 4.01% by the year 2050, and the projected number of AF patients was estimated to be 730,431 in Taiwan (Figure 4).

The short-term, intermediate-term and lifetime risks of AF for subjects at different ages are shown in Table 1. For Chinese adults aged ≥20 years, the lifetime risk of AF was appropriately 1 in 7, being higher for males (1 in 6) compared to females (1 in 7) (Table 2).

Risk of adverse events among AF patients and the time trends

Cumulative incidence curves of adverse events for AF patients are shown in Figure 5, while the annual risks of various adverse events after AF was diagnosed is shown in Figure 6. The annual risks were 9.17% for mortality, 8.53% for heart failure, 3.40% for ischemic stroke, 2.22% for dementia, 1.05% for sudden cardiac death and 0.51% for myocardial infarction.

The baseline characteristics of patients with or without AF are shown in Table 3. As expected, AF patients had more comorbidities than non-AF patients. Compared to patients without AF, AF was associated with an increased risk of mortality (adjusted hazard ratio 2.61, 95%CI 2.58-2.64), heart failure (3.31, 3.26-3.36), ischaemic stroke (3.34, 3.26-3.42), dementia (1.56, 1.53-1.59), sudden cardiac death (1.83, 1.77-1.89), and myocardial infarction (1.62, 1.53-1.72); all p value <0.01 (Figure 6). The adjusted HRs of each events compared to patients without AF with mortality being the competing risk are also shown in Figure 6.

Figure 7 shows the HRs of mortality, heart failure and ischemic stroke of AF patients compared to patients without AF for different time periods after AF was diagnosed. The risk of events of AF patients was especially higher than non-AF patients within the initial period (6 months) after AF was diagnosed (HR = 13.28, 95%CI 10.89-16.20 <within 6 months> versus 3.31, 95%CI 3.23-3.39 <after 6 months>, p value <0.001 for ischemic stroke; HR = 5.86, 95%CI 5.25-6.55 <within 6 months> versus 3.05, 95%CI 3.00-3.09 <after 6 months>, p value <0.001 for heart failure). The one-year risk of adverse events after incident AF in each year remained broadly similar (Figure 8).

Discussion

Our principal findings in this large nationwide cohort study of a Chinese population, are as follows: (i) The incidence of AF was 1.51 per 1000 person-years in year 2011, with a lifetime risk of AF being appropriately 1 in 6 for males and 1 in 7 for females aged ≥20 years; (ii) The prevalence of AF was 1.07% in 2011, and is estimated to be 4.01% in 2050; and (iii) Compared to patients without AF, AF was associated with an increased risk of mortality, heart failure, ischaemic stroke, dementia, sudden cardiac death, and myocardial infarction.

Incidence, prevalence, lifetime risk of projection number of AF

As far as we are aware, this is the largest and most comprehensive insight into the incidence, prevalence, lifetime risk and projected number of AF among Asians. In a recent review of the AF epidemiology in Asia, the incidence rate of AF was around 5.38 per 1000 person-years based on the data of 10 studies which included 8,190 incident AF patients.[19] Most of the studies included in this systemic review enrolled specific populations, such as hyperuricemia, hyperlipidemia, osteoporosis, underweight, heavy alcohol consumption, and the elderly, and therefore, the incidence rate of AF may be overestimated and could not be generalized to general Asian population.

Most prior data on AF incidence rates came from studies performed in Europe and North America. For example, the Rotterdam study enrolled subjects aged 55 years and above, where the AF incidence rate was around 9.9/1000 person-years.[3] In a recent report from Netherlands studied subjects aged 28 to 75 years old, where the incidence rate of AF was 3.3/1000 person-years.[20] The reported incidence rate of AF ranged between 3.3 to 19.2 per 1000 person-years among predominantly United States-based cohorot studies.[3,21-24] In the present study, the AF incidence of Chinese population was around 1.51 per 1000 person-

years, is lower compared to that of Caucasians. Also, the lifetime risk which was estimated based on the AF incidence rate for Chinese (1 in 6 for males and 1 in 7 for females) in the present study was lower than that reported from the Western countries (e.g. 1 in 4 in the Framingham Heart Study).[2]

The prevalence rate of AF in our Chinese cohort was around 1.07% in year 2011, which substantially increased with age. Similar to the growing burden of AF all over the world,[25] the AF prevalence and the absolute number of AF patients will continuously increase in the coming decades in Taiwan based on the projected estimations. We have showed a clear trend demonstrating that incident AF patients were not only becoming older but having more comorbidities. It may suggest that although aging population and longer life expectancy are important reasons responsible for the increase in AF prevalence, the concurrent increase in hypertension, heart failure and other systemic diseases which are also more prevalent in the elderly may also contribute.

In previous community studies, the AF prevalence rate ranged from 0.7% to 1.6% in Asia (0.7% in Korea,[26] 1.5% in Singapore,[27] and 1.6% in Japan[28]). Similar to the incidence rate, the prevalence rate of AF in Asians was generally lower compared to the reported AF prevalence rates in Caucasians (e.g. 5.5% in Rotteram study).[3,25] Although the precise mechanisms behind the differences of AF epidemiology between Asians and Caucasians remain unclear, part of the global variation may be attributable to a better surveillance in developed countries, and the prevalence of AF in some Asian countries is probably underestimated.[25,29] Besides, the longer life expectancy and more prevalent cardiovascular risk factors and diseases, including smoking, obesity, hypertension, ischemic heart diseases and diabetes, in the developed western countries may also play important roles.[29] Furthermore, variants at several genetic loci are associated with the development of AF and

seem to differ in frequency between populations, and are likely to explain some of the ethnic variation observed in the prevalence of AF.[29-31]

Risk of adverse events of Asian AF patients

AF is associated with an increased risk of several adverse events other than ischemic stroke. In a recent meta-analyses which included 104 cohort studies involving 587,867 AF patients, AF was associated with an increased risk of all-cause mortality (relative risk [RR] 1.46), ischemic stroke (RR 2.33), ischemic heart disease (RR 1.61), sudden cardiac death (RR 1.88), heart failure (RR 4.99), chronic kidney disease (1.64), and peripheral arterial disease (1.31).[32] Again, most of the studies included in this meta-analysis mainly enrolled Caucasians, and data about the risk of adverse events associated with AF in Asians are limited.

Compared to the data mainly from non-Asians,[32] the relative risks associated with AF in Asians were generally higher for ischemic stroke (3.34 versus 2.33), and mortality (2.61 versus 1.46); lower for heart failure (3.31 versus 4.99); and similar for sudden cardiac death (1.83 versus 1.88) and myocardial infarction (1.62 versus 1.61). We demonstrated that the risks of ischemic stroke, heart failure and mortality were especially higher compared to non-AF patients within the initial period (approx. 6 months) after AF was first diagnosed. During this vulnerable period, comprehensive evaluation and proactive management of associated comorbidities should be performed.

Although the risk of ischemic stroke associated with AF compared to non-AF patients is higher than other events in our cohort with an adjusted HR of 3.34, the annual risks of mortality (9.17%/year) and heart failure (8.53/year) were higher than that of ischemic stroke (3.40%/year). In the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, the majority of deaths are not related to stroke among the anticoagulated AF

population.[33] In a recent study from the Loire Valley AF project, cardiovascular deaths accounted for 54% and non-cardiovascular for 43% of deaths for AF patients.[34] The three main causes of death were heart failure (29%), infection (18%), and cancer (12%), and only 7% died from stroke. Thus, optimization of management of any underlying heart disease and associated comorbidities should be part of the holistic management approach to improve patient care in AF.

Time trends of risk scores and risks of adverse events

In the present study, we demonstrated that the risk of adverse events of AF patients remained similar and did not decrease over the study period despite improvements in our understanding and management of AF. Nonetheless, only around 15% of AF patients received appropriate treatments of stroke prevention according to the guideline recommendations in Taiwan.[35] Also, more than 50% of AF patients did not receive rate control treatment which was associated with a lower risk of mortality.[36] We also found that the baseline stroke scores of newly-diagnosed AF patients were increasingly higher with each subsequent year, which may reflect greater longevity and improved detection of risk factors.

Study limitations

There are several limitations in the present study, given the natures of the nationwide registry dataset we used. First, the subtypes of AF (paroxysmal or non-paroxysmal) were not available. Second, the diagnoses of AF and adverse events were based on the ICD-9-CM codes registered by physicians responsible for the care of the patients, and no direct evaluations for events were performed. Although the diagnostic accuracies of AF, heart failure, myocardial infarction and ischemic stroke in Taiwan NHIRD have been validated,[12,13,16-18] the diagnostic accuracies of these diseases in an insurance database may

not be as accurate as that of electronic medical records. Third, we investigated the risk of ischemic stroke and myocardial infarction among patients who did not receive antithrombotic therapies within 90 days after incident AF. Since patients may receive antithrombotic therapies during the follow up, the true risk of ischemic stroke and myocardial infarction without treatment of AF patients may be higher than we reported here. Fourth, the lifetime risk and prevalence projection of AF were estimated using the data collected from year 2000 to 2011 without considering effects of birth-cohort and changes in population demographics and other comorbidities associated with the occurrence of AF. Also, the projected prevalence rate and patient number of AF were estimated based on and sensitive to several assumptions of the model, such as $RR_{AF} = 2.61$, $q = 0$, etc. Fifth, although we have shown a higher AF prevalence rate among older patients, we were not able to clearly analyze how much of this increase is due to concurrent increases in hypertension, heart failure or other comorbidities in the elderly. Last, the present study only enrolled Chinese patients, whether the results can be extrapolated to other populations remains uncertain.

Conclusion

The burden of AF amongst Asian patients is increasing, with a lifetime risk of AF being appropriately 1 in 7. This results in a significant mortality, heart failure, ischaemic stroke, dementia, sudden cardiac death and myocardial infarction. Optimized management of any associated comorbidities should be part of the holistic management approach for AF.

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Author Contributions

Study concept and design: Tze-Fan Chao, Chia-Jen Liu, Gregory Y. H. Lip, Shih-Ann Chen

Acquisition of data: Chia-Jen Liu, Tzeng-Ji Chen

Analysis and interpretation of data: Tze-Fan Chao, Ming-Hsiung Hsieh

Drafting of the manuscript: Tze-Fan Chao, Gregory Y. H. Lip

Critical revision of the manuscript for important intellectual content: Gregory Y. H. Lip, Shih-Ann Chen

Statistical analysis: Tze-Fan Chao, Chia-Jen Liu

Study supervision: Ming-Hsiung Hsieh, Gregory Y. H. Lip, Shih-Ann Chen

Dr. Tze-Fan Chao and Prof. Gregory Y.H. Lip are guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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Table 1. Baseline demographic and clinical characteristics of incident AF

Variables	Overall 2000-2011 (n = 289,559)	2000 - 2003 (n = 88,341)	2004 - 2007 (n = 96,673)	2008 - 2011 (n =104,545)	P value
Age (years), mean (SD)	71.5 (13.3)	70.9 (12.8)	71.5 (13.3)	71.9 (13.6)	< 0.001
Distribution of age, n (%)					< 0.001
20–29 years old	1,804 (0.6)	553 (0.6)	629 (0.7)	622 (0.6)	
30–39 years old	4,615 (1.6)	1,493 (1.7)	1,491 (1.5)	1,631 (1.6)	
40–49 years old	13,970 (4.8)	4,375 (5.0)	4,796 (5.0)	4,799 (4.6)	
50–59 years old	31,909 (11.0)	8,656 (9.8)	10,765 (11.1)	12,488 (11.9)	
60–69 years old	55,545 (19.2)	18,275 (20.7)	18,133 (18.8)	19,137 (18.3)	
70–79 years old	95,191 (32.9)	32,267 (36.5)	32,091 (33.2)	30,833 (29.5)	
≥ 80 years old	86,525 (29.9)	22,722 (25.7)	28,768 (29.8)	35,035 (33.5)	
Gender (male), n (%)	160,185 (55.3)	49,249 (55.7)	53,207 (55.0)	57,729 (55.2)	0.006
Comorbidities, n (%)					
Hypertension	214,448 (74.1)	59,363 (67.2)	72,896 (75.4)	82,189 (78.6)	< 0.001
Diabetes mellitus	89,440 (30.9)	21,641 (24.5)	30,280 (31.3)	37,519 (35.9)	< 0.001
Congestive heart failure	122,819 (42.4)	36,033 (40.8)	41,698 (43.1)	45,088 (43.1)	< 0.001
Previous stroke/transient ischemic attack	107,555 (37.1)	28,040 (31.7)	36,846 (38.1)	42,669 (40.8)	< 0.001
Previous vascular diseases	75,251 (26.0)	16,275 (18.4)	25,792 (26.7)	33,184 (31.7)	< 0.001
$CHADS_2$ score, mean (SD)	2.69 (1.67)	2.40 (1.57)	2.74 (1.66)	2.89 (1.71)	< 0.001
CHA_2DS_2-VASc score, mean (SD)	4.14 (2.10)	3.77 (1.95)	4.20 (2.10)	4.39 (2.19)	< 0.001
Follow-up (years), mean (SD)	3.72 (3.24)	5.82 (4.02)	4.11 (2.44)	1.58 (1.17)	

SD = standard deviation

Table 2. Age-specific short- and intermediate-term and lifetime risk estimates for atrial fibrillation

Index Age (Years)	Short- and Intermediate-Term Risk of AF							Lifetime Risk	
	10 years	20 years	30 years	40 years	50 years	60 years	70 years		
All									
20-29	0.05(0.04-0.06)	0.18(0.16-0.19)	0.53(0.50-0.55)	1.44(1.40-1.48)	2.90(2.84-2.96)	5.13(5.05-5.20)	7.33(7.24-7.42)	7.84(7.75-7.93)	1 to 13
30-39	0.11(0.10-0.12)	0.42(0.40-0.44))	1.23(1.20-1.27)	2.52(2.47-2.57)	4.49(4.43-4.56)	6.44(6.36-6.52)		6.89(6.81-6.97)	1 to 15
40-39	0.33(0.31-0.35)	1.19(1.16-1.23)	2.56(2.51-2.62)	4.66(4.59-4.73)	6.74(6.65-6.82)			7.21(7.13-7.30)	1 to 14
50-59	0.96(0.93-0.99)	2.49(2.44-2.54)	4.83(4.76-4.90)	7.14(7.05-7.23)				7.67(7.58-7.77)	1 to 13
60-69	2.74(2.67-2.82)	6.94(6.82-7.06)	11.08(10.93-11.23)					12.02(11.88-12.19)	1 to 8
70-79	6.75(6.60-6.90)	13.42(13.21-13.66)						14.96(14.73-15.18)	1 to 7
≥ 80	13.9(13.6-14.2)							21.67(20.35-22.99)	1 to 5
Total								15.11(14.93-15.29)	1 to 7
Male									
20-29	0.07(0.05-0.08)	0.24(0.22-0.26)	0.73(0.69-0.77)	1.93(1.87-2.00)	3.70(3.61-3.79)	5.97(5.85-6.08)	8.16(8.03-8.30)	8.58(8.45-8.72)	1 to 12
30-39	0.16(0.14-0.18)	0.61(0.57-0.64)	1.70(1.65-1.76)	3.32(3.24-3.40)	5.39(5.28-5.49)	7.39(7.27-7.52)		7.78(7.65-7.90)	1 to 13
40-39	0.47(0.44-0.50)	1.61(1.55-1.67)	3.30(3.22-3.38)	5.46(5.35-5.57)	7.56(7.43-7.68)			7.96(7.83-8.08)	1 to 13
50-59	1.28(1.23-1.34)	3.17(3.08-3.25)	5.59(5.47-5.70)	7.94(7.80-8.07)				8.38(8.24-8.52)	1 to 12
60-69	3.46(3.33-3.58)	7.89(7.70-8.07)	12.19(11.96-12.41)					13.00(12.77-13.24)	1 to 8
70-79	7.49(7.26-7.72)	14.75(14.43-15.08)						16.13(15.80-16.47)	1 to 6
≥ 80	13.9(13.4-14.3)							20.75(19.24-22.26)	1 to 5
Total								16.92(16.66-14.20)	1 to 6
Female									
20-29	0.03(0.02-0.04)	0.11(0.10-0.13)	0.32(0.29-0.34)	0.95(0.90-1.00)	2.10(2.03-2.16)	4.29(4.19-4.38)	6.49(6.37-6.61)	7.09(6.97-7.21)	1 to 14
30-39	0.07(0.06-0.08)	0.25(0.22-0.27)	0.79(0.75-0.83)	1.77(1.71-1.83)	3.65(3.57-3.74)	5.54(5.44-5.65)		6.06(5.95-6.16)	1 to 17
40-39	0.19(0.17-0.21)	0.78(0.74-0.82)	1.84(1.78-1.91)	3.88(3.79-3.97)	5.93(5.82-6.04)			6.49(6.37-6.60)	1 to 15
50-59	0.65(0.61-0.69)	1.83(1.77-1.90)	4.09(4.00-4.19)	6.37(6.25-6.49)				6.89(6.86-7.11)	1 to 14
60-69	2.08(1.99-2.17)	6.05(5.90-6.21)	10.05(9.86-10.25)					11.14(10.93-11.35)	1 to 9
70-79	6.12(5.93-6.32)	12.29(12.01-12.56)						13.95(13.66-14.24)	1 to 7
≥ 80	13.9(13.5-14.4)							21.86(20.03-23.69)	1 to 5
Total								14.63(14.38-14.89)	1 to 7

Table 3. Baseline demographic and clinical characteristics of AF and non-AF populations

Variables	AF population (n = 289,559)	Non-AF population (n = 289,559)	P value
Age (years), mean (SD)	71.5(13.3)	71.5(13.3)	0.995
Distribution of age, n (%)			1.000
20–29 years old	1,804 (0.6)	1,804 (0.6)	
30–39 years old	4,615 (1.6)	4,615 (1.6)	
40–49 years old	13,970 (4.8)	13,970 (4.8)	
50–59 years old	31,909 (11.0)	31,909 (11.0)	
60–69 years old	55,545 (19.2)	55,545 (19.2)	
70–79 years old	95,191 (32.9)	95,191 (32.9)	
≥ 80 years old	86,525 (29.9)	86,525 (29.9)	
Gender (male), n (%)	160,185 (55.3)	160,185 (55.3)	1.000
Comorbidities, n (%)			
Hypertension	214,448 (74.1)	161,012 (55.6)	< 0.001
Diabetes mellitus	89,440 (30.9)	68,845 (23.8)	< 0.001
Congestive heart failure	122,819 (42.4)	34,180 (11.8)	< 0.001
Previous stroke/transient ischemic attack	107,555 (37.1)	47,552 (16.4)	< 0.001
Previous vascular diseases	75,251 (26.0)	14,286 (4.9)	< 0.001
$CHADS_2$ score, mean (SD)	2.69 (1.67)	1.72 (1.25)	< 0.001
CHA_2DS_2-VASc score, mean (SD)	4.14 (2.10)	2.95 (1.92)	< 0.001
Follow-up (years), mean (SD)	3.72 (3.24)	4.73 (3.29)	< 0.001

SD = standard deviation

Figure Legends

Figure 1. $CHADS_2$ and CHA_2DS_2-VASc scores of incident AF patients in each year. The $CHADS_2$ and CHA_2DS_2-VASc scores of incident AF patients diagnosed in each year showed a trend to became higher with successive year.

Figure 2. Incidence rate of AF stratified by age and sex. The incidence rates of AF form year 2000 to 2011 are shown in Figure 2A. The incidence of AF in year 2011 was 1.51 per 1000 person-years (Figure 2A), with a stepwise increase with age (Figure 2B). AF = atrial fibrillation.

Figure 3. Prevalence rate of AF stratified by age and sex. The prevalence rate of AF continuously increased from 0.46% to 1.07% during the 12 years, with a 2.33-fold increase (Figure 3A). The prevalence rate substantially increased for subjects aged above 60 years (Figure 3B). AF = atrial fibrillation.

Figure 4. The projection number and prevalence rate of AF. The projected prevalence rate of AF continuously increases to 4.01% in year 2050, and there will be 730,431 AF patients in Taiwan. AF = atrial fibrillation.

Figure 5. Cumulative incidence curves of adverse events.

*The risks of different adverse events were investigated among different subpopulations, as mentioned in the method section.

Figure 6. The annual risks of adverse events of AF patients and the hazard ratios

compared to patients without AF. The annual risk of adverse events ranged from 0.51% for myocardial infarction to 9.17% for mortality. Compared to patients without AF, AF was associated with a 1.56- to 3.34-fold increase of various events after the adjustment for age, gender and comorbidities.

*The risks of different adverse events were investigated among different subpopulations, as mentioned in the method section.

Figure 7. Risk of mortality, heart failure and ischemic stroke of AF patients compared to non-AF patients in different time periods. The risk of events of AF patients was especially higher than non-AF patients within the initial period after AF was diagnosed.

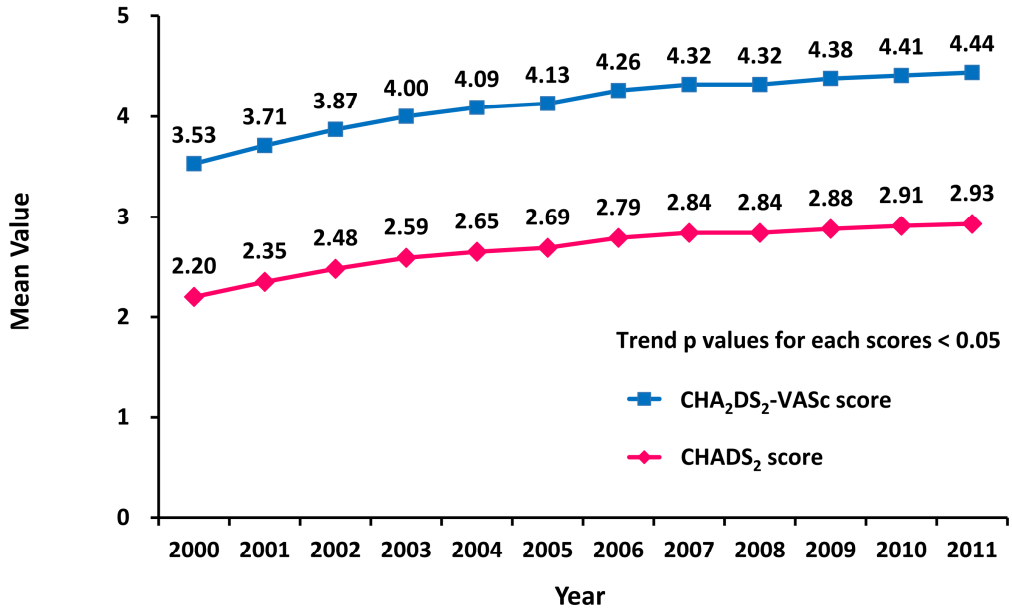
*The risks of different adverse events were investigated among different subpopulations, as mentioned in the method section.

Figure 8. Trend of 1-year risk of adverse events after AF was diagnosed in each year. The one-year risk of adverse events after incident AF in each year remained broadly similar.

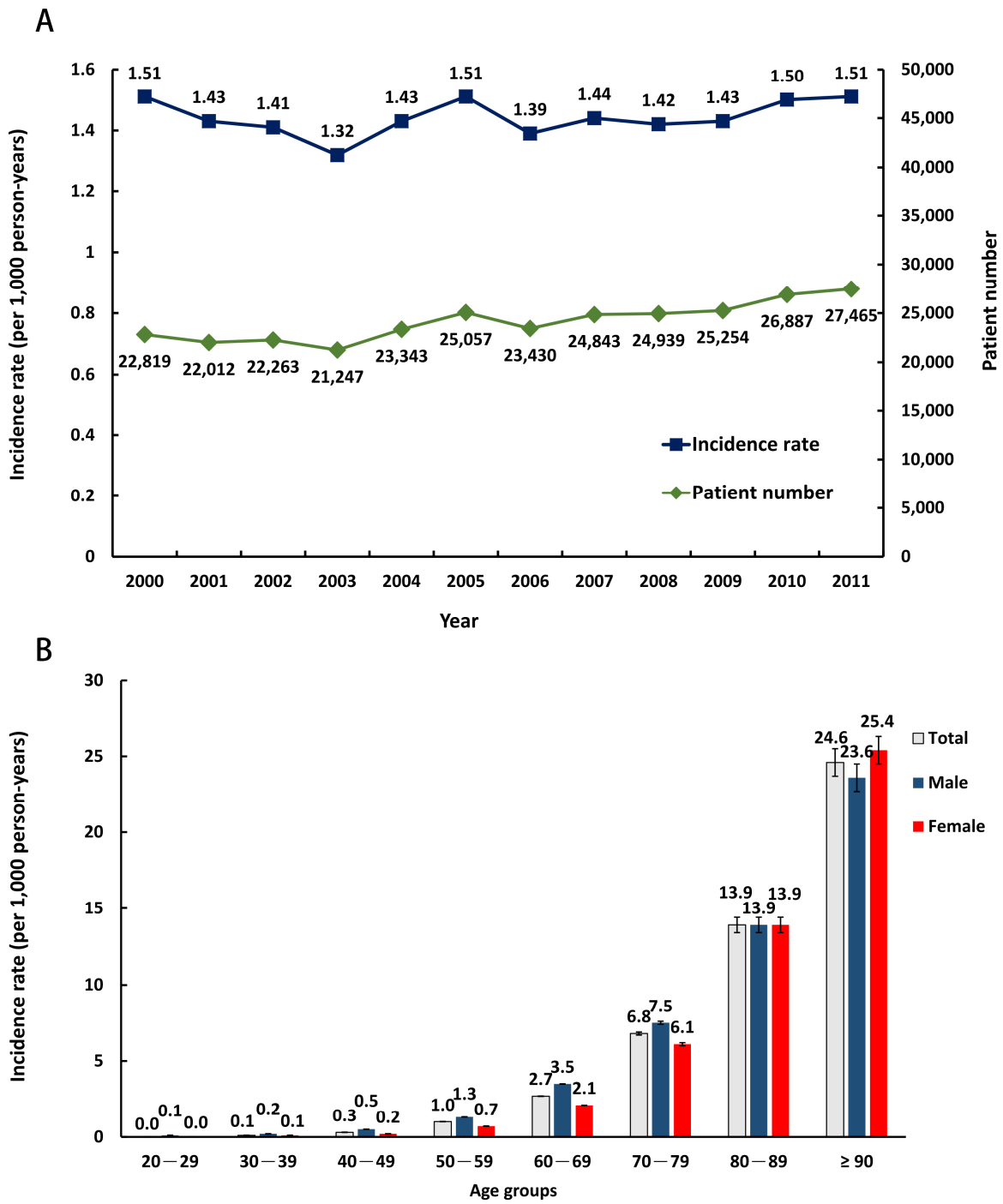
*The risks of different adverse events were investigated among different subpopulations, as mentioned in the method section.

Supplemental Table 1. Number of new-onset AF and person-years of follow up in each year

Year	Number of New-onset AF	Person-years
2000	22,819	15,088,006
2001	22,012	15,441,420
2002	22,263	15,794,581
2003	21,247	16,067,287
2004	23,343	16,349,526
2005	25,057	16,627,835
2006	23,430	16,888,511
2007	24,843	17,276,161
2008	24,939	17,516,335
2009	25,254	17,719,832
2010	26,887	17,934,672
2011	27,465	18,170,918



CHA_2DS_2-VASc score	Mean	3.53	3.71	3.87	4.00	4.09	4.13	4.26	4.32	4.32	4.38	4.41	4.44
	SD	1.85	1.94	1.98	2.01	2.06	2.08	2.10	2.13	2.16	2.18	2.19	2.21
$CHADS_2$ score	Mean	2.20	2.35	2.48	2.59	2.65	2.69	2.79	2.84	2.84	2.88	2.91	2.93
	SD	1.51	1.56	1.59	1.61	1.64	1.65	1.67	1.68	1.70	1.70	1.71	1.71


A
Incidence rate (per 1,000 person-years)
Patient number
1.51
1.43
1.41
1.32
1.43
1.51
1.39
1.44
1.42
1.43
1.50
1.51
22,819
22,012
22,263
21,247
23,343
25,057
23,430
24,843
24,939
25,254
26,887
27,465
Incidence rate
Patient number
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Year
B
Incidence rate (per 1,000 person-years)
0.0
0.1
0.0
0.1
0.2
0.1
0.3
0.5
0.2
1.0
1.3
0.7
2.7
3.5
2.1
6.8
7.5
6.1
13.9
13.9
13.9
24.6
23.6
25.4
Total
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Female
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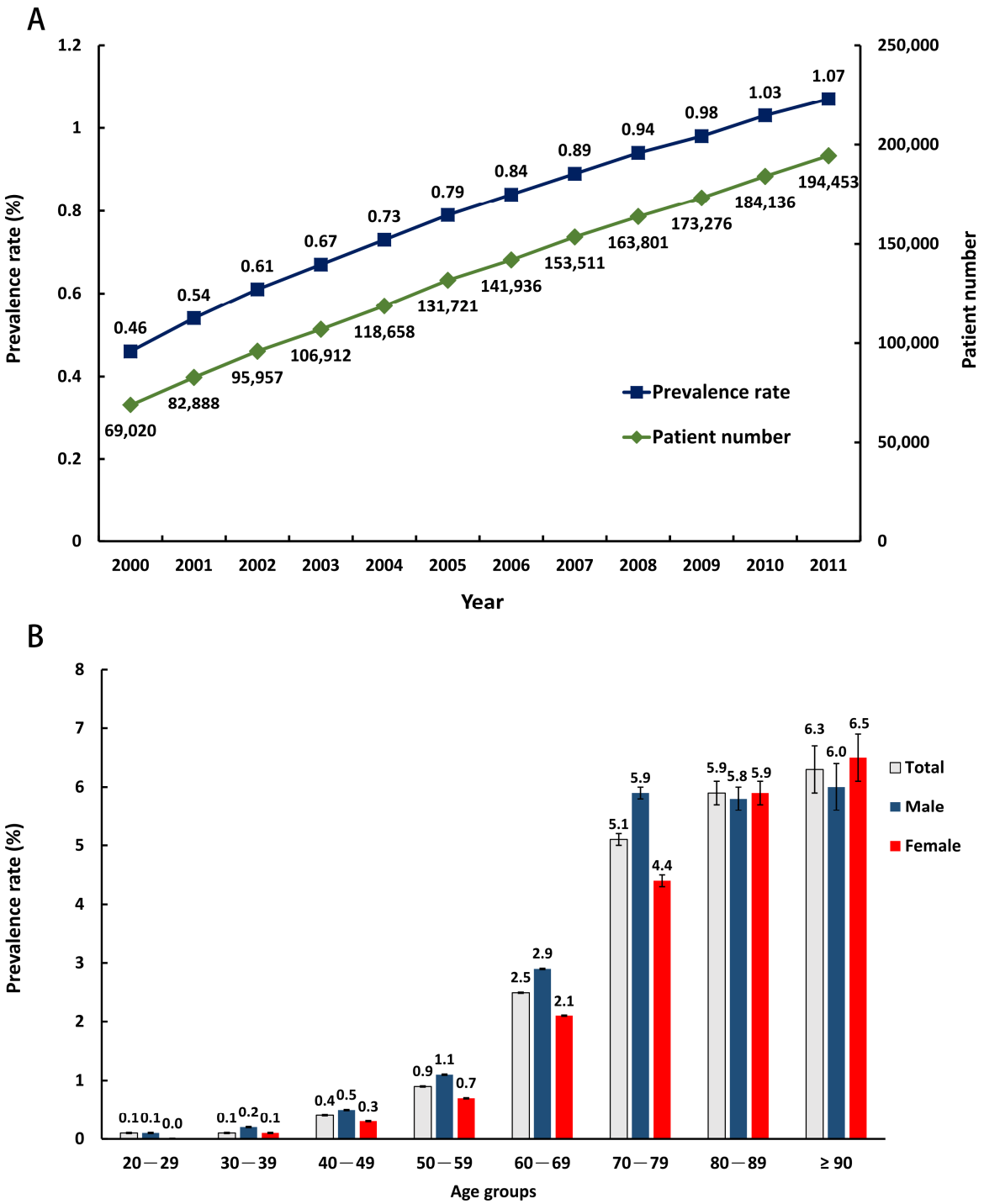
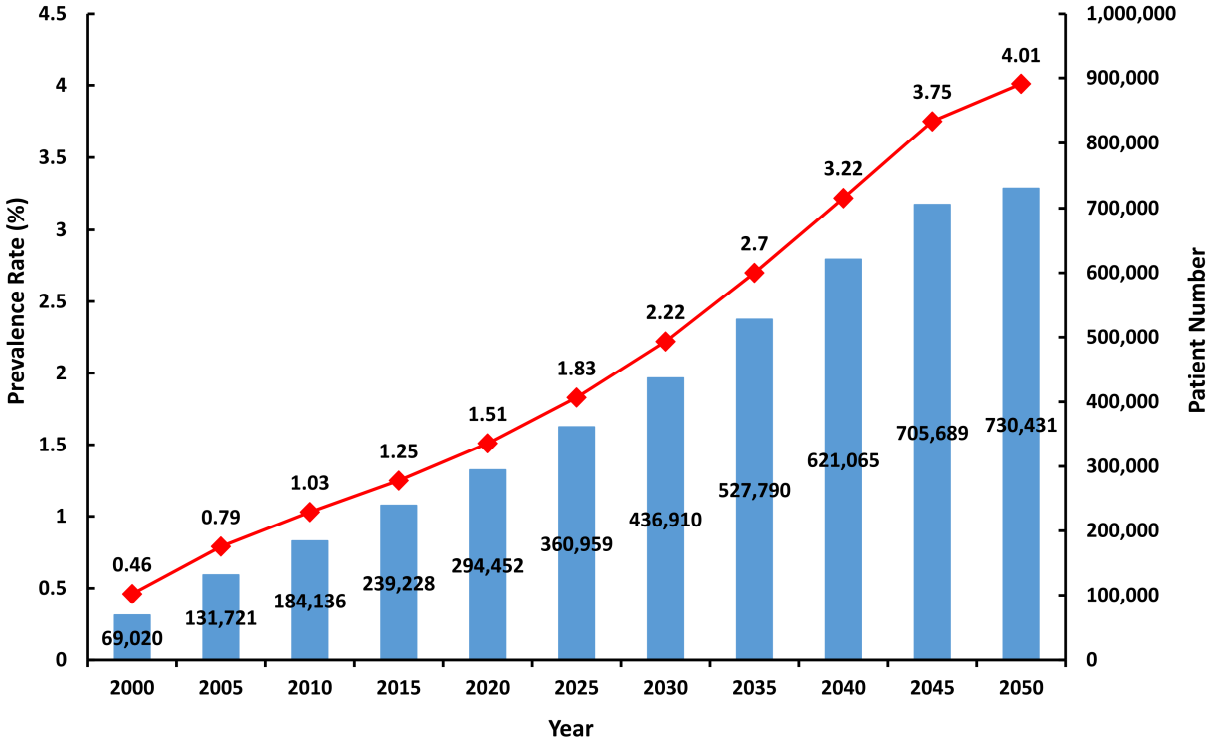
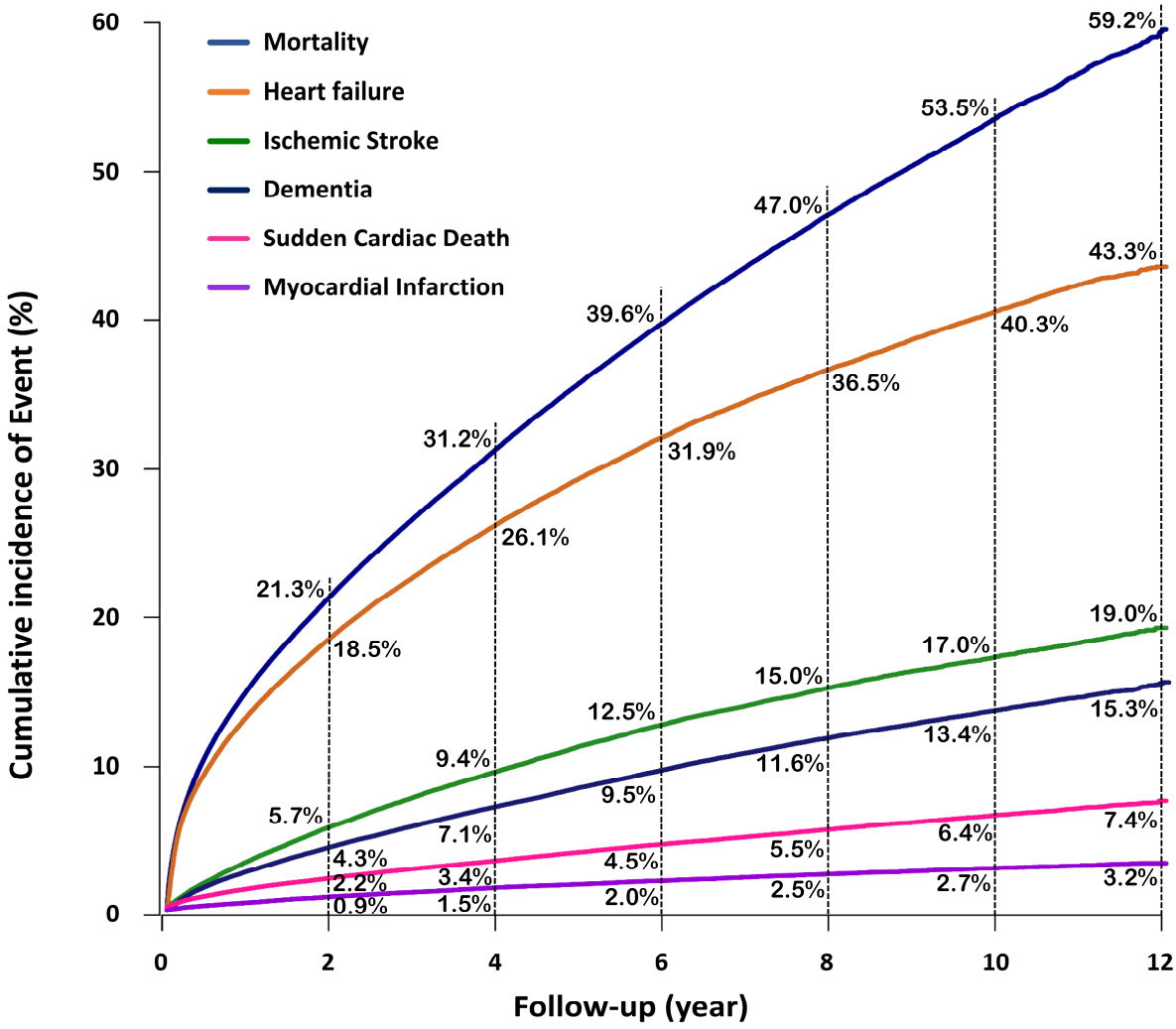
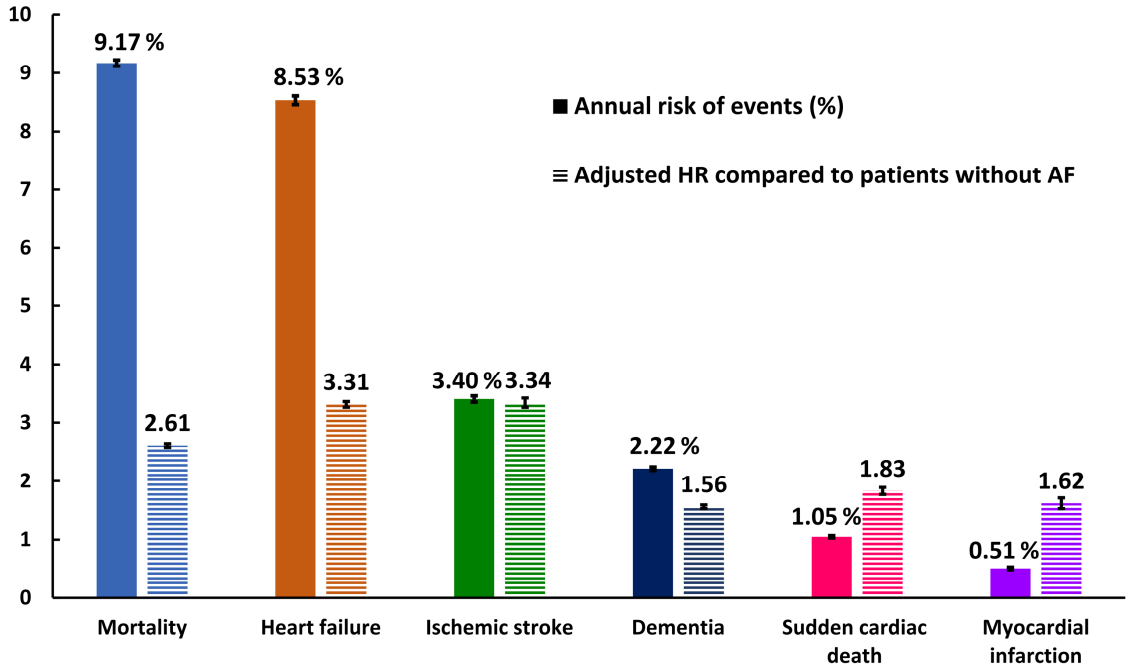
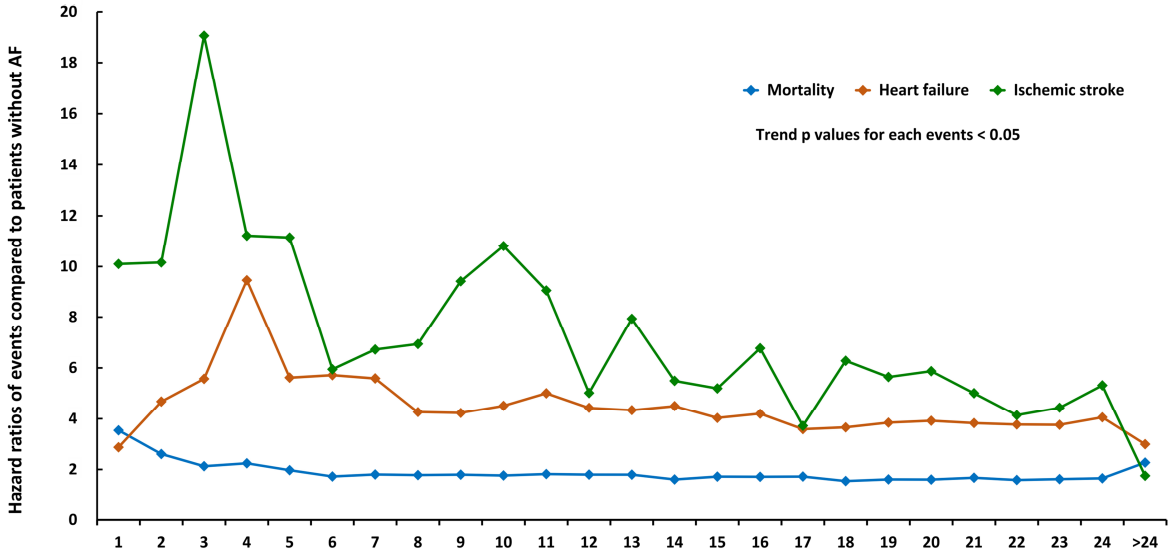
30—39
40—49
50—59
60—69
70—79
80—89
≥ 90
Age groups


A
Prevalence rate (%)
Patient number
Year
Prevalence rate
Patient number
0.46
0.54
0.61
0.67
0.73
0.79
0.84
0.89
0.94
0.98
1.03
1.07
69,020
82,888
95,957
106,912
118,658
131,721
141,936
153,511
163,801
173,276
184,136
194,453
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
B
Prevalence rate (%)
Age groups
Total
Male
Female
20—29
30—39
40—49
50—59
60—69
70—79
80—89
≥ 90
0.1 0.1 0.0
0.1 0.2 0.1
0.4 0.5 0.3
0.9 1.1 0.7
2.5 2.9 2.1
5.1 5.9 4.4
5.9 5.8 5.9
6.3 6.0 6.5

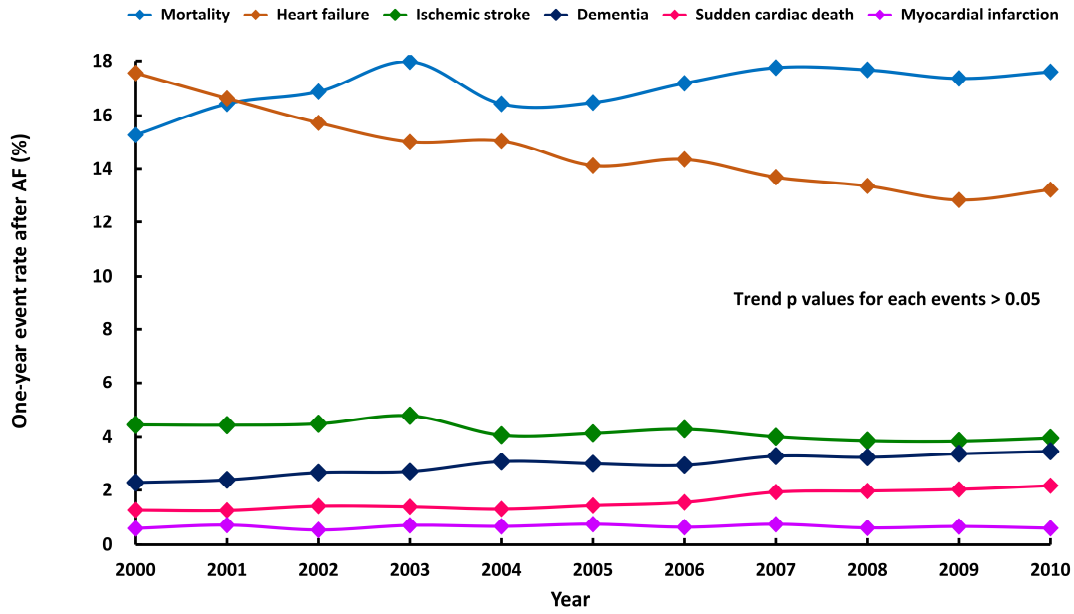








Hazard ratio	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	>24
Mortality	3.54	2.61	2.13	2.24	1.97	1.73	1.80	1.78	1.80	1.76	1.82	1.80	1.80	1.61	1.72	1.71	1.72	1.54	1.61	1.60	1.68	1.59	1.62	1.65	2.27
Heart failure	2.87	4.69	5.57	9.46	5.62	5.72	5.59	4.27	4.23	4.52	5.01	4.44	4.35	4.51	4.03	4.20	3.59	3.66	3.85	3.92	3.83	3.77	3.76	4.06	3.00
Ischemic stroke	10.10	10.16	19.07	11.22	11.15	5.95	6.72	6.94	9.42	10.81	9.05	5.02	7.93	5.49	5.20	6.77	3.72	6.28	5.64	5.87	5.01	4.14	4.44	5.32	1.75



Mortality	15.28	16.43	16.88	17.98	16.43	16.48	17.19	17.76	17.68	17.37	17.61
Heart failure	17.57	16.63	15.73	15.02	15.04	14.12	14.35	13.69	13.37	12.84	13.23
Ischemic stroke	4.45	4.43	4.48	4.78	4.06	4.13	4.28	4.00	3.86	3.84	3.95
Dementia	2.28	2.38	2.65	2.70	3.08	3.00	2.94	3.28	3.24	3.37	3.47
Sudden cardiac death	1.27	1.26	1.41	1.39	1.31	1.44	1.55	1.93	1.97	2.03	2.16
Myocardial infarction	0.59	0.71	0.53	0.70	0.66	0.74	0.63	0.74	0.61	0.66	0.60