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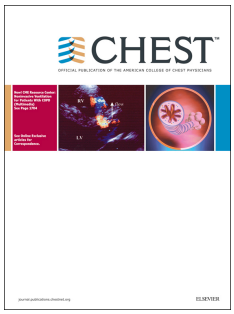

The Global Burden of Atrial Fibrillation and Stroke: A Systematic Review of the Clinical Epidemiology of Atrial Fibrillation in Asia

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The Global Burden of Atrial Fibrillation and Stroke:

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Short title The Global Burden of Atrial Fibrillation

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Abbreviations

ACS - acute coronary syndrome

AF – atrial fibrillation

AHF - acute heart failure

AMI - acute myocardial infarction

CI - confidence interval

CKD - chronic kidney disease

COPD - chronic obstructive pulmonary disease

DM - diabetes mellitus

HPT - hypertension

IS - ischemic stroke

MOOSE - Meta-analyses of Observational Studies in Epidemiology

NOAC - non-vitamin K antagonist oral anticoagulants

OAC - oral anticoagulants

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analyses

Abstract

Background: Our previous review showed great variability on the incidence and prevalence of atrial fibrillation (AF) in non-Western cohorts, especially from Asian countries; in recent years, epidemiology studies on AF have been increasingly reported.

Methods: We therefore conducted an updated systematic review, to present the current knowledge base of AF epidemiology in Asian countries since our prior review. We also explored AF incidence and the risk of stroke in AF using meta-analysis, with I^2 testing the heterogeneity. Third, 'real world' antithrombotic drug use for ischemic stroke (IS) prevention associated with AF was studied.

Results： 58 papers from 8 countries in Asia were finally included in our analysis. The summary annual incidence of AF was 5.38 (95% CI: 4.53-6.24, I^2=99.5%, N=10) per 1000 person-years and the IS annual risk in AF was 3.0% (1.60%-4.95%, I^2=99.8%, N=8) when meta-analysis was performed on hospital- and community-based studies. Hospital- and community- based AF prevalence ranged from 0.37% to 3.56% and 2.8% to 15.8%, respectively. IS prevalence in AF ranged 1.9-6.0% and 0.36-28.3% in community and hospital studies, respectively. Warfarin use in Chinese is relatively low (1.0-4.1%) when compared with Japanese (49.1-70.0%) in community-based studies. The rate of warfarin use was <50% in hospital-based studies.

Conclusions: AF incidence and prevalence has increased in recent years, though great variability still exists in Asian countries. Variability in annual IS risk in AF patients was apparent between hospital- and community-based studies. However, the rate of warfarin use was less than 50% in hospital studies from Asian countries.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and is associated with an increased risk of stroke,[1] heart failure[2] and mortality.[3] Much of AF epidemiology has been derived from Western cohorts in North America and Europe, but data from non-Western cohorts are increasing, and published in our systematic review conducted five years ago.[1]

Our previous systematic review showed great variability on the incidence and prevalence of AF in non-Western cohorts, especially from Asian countries.[4,5] In recent years, epidemiology studies on AF have been increasingly reported from Asia.

We therefore conducted an updated systematic review, to present the current knowledge base of AF epidemiology by systematically reviewing the published literature in Asian countries in the recent five years, since our prior review. We also explored AF incidence and the risk of stroke in AF among Asian countries using meta-analysis. Third, 'real world' antithrombotic drug use for ischemic stroke (IS) prevention associated with AF was studied.

Materials and Methods

Methods for our review were reported previously[1], and this update replicates our previous approach. We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines, when performing this study.[6,7] In brief, two reviewers (Y. B. and A. S.) searched PubMed for studies published from 1 January, 2011 to 19 September, 2016 using “atrial fibrillation”, ”epidemiology”, “prevalence”, “incidence”, “risk factors”, “stroke”, “thromboembolism”, “transient ischemic attack” and names of countries in Asia according to the definitions from World Health Organization. We also listed the incidence and prevalence of AF categorized by hospital- or community-based studies.[1] Furthermore, risk factors for AF, risk of ischemic stroke (IS) in AF and antithrombotic therapy used for stroke prevention in AF were explored in our study. AF, including atrial flutter or not, was defined according to the definitions in the original papers. The same exclusion criteria were used for our search, including cohort size < 750, inclusion of diseases other than AF, and clinical trials, except for the language exceptions. Studies using both English and Chinese were eligible for our study. Studies using duplicate data source would be excluded except for the one with the longest follow-up or with the most recent or the main publications or during different periods or with additional data relevant to our study.

We extracted the following baseline information from the studies except for the main objectives, such as authors, cohort size, inclusion criteria, study design, study period.

Statistical analysis

STATA, version 12.0 (Stata Corp.) and Medcalc, version 16.5 were used for statistical analyses. The formula event rate = counts of events /person-years of observation was used in our meta-analysis. Mean follow-up period and number of included patients were multiplied to calculate person-years if not reported in the original papers. The third variable would be estimated in case of the other two provided variables. 95% confidence interval of event rate was calculated using Medcalc. Outcomes were compared using a fixed effects model or, random effects model according to whether heterogeneity was found. I^2 index was used to quantify heterogeneity across studies,[8] with values of $\leqslant$ 25%, 25% to 50%, and $\geqslant$50% representing low, moderate and high degrees of heterogeneity, respectively. Begg's correlation test was used to assess publication bias.[9,10] Weighted regression of AF rates from community-based studies in relation to increasing age was performed to show the AF rate trends with age. A two-sided p value<0.05 was taken as statistically significant.

Results

A flow-chart for the search process is shown in **Figure 1**. Of the identified papers, we included 58 studies from the initial 821 abstracts, including 23 hospital-based papers and 35 community-based papers. The included papers were categorized based on studied countries, as Chinese cohorts(mainland China, Taiwan, Hongkong)28, Japan 13, South Korea 5, Middle East 5, Bahrain 1, India 3, Malaysia 1, and Turkey 2.

Incidence of AF

The summary annual incidence of AF was 5.38 (95% confidence interval [CI]: 4.53-6.24) per 1000 person-years through meta-analyzing 8,190 AF and 3,883,205 person-years data from Asian countries (mainly from Chinese, Japanese and Korean) **(e- Figure 1 and Table 1).** No publication bias was observed according to Begg's test (p=0.79). The pooled AF annual incidence in community-based studies was 4.70 (95% CI: 3.84-5.56) per 1000 person-years, after excluding two studies reporting the incidence of new-onset AF in hospital-based studies. One study from Japan showed that annual incidence of hospital-based AF was 9.4 per 1000 person-year.[11] The one study from South Korea showed AF incidence was 11.4 and 8.9 per 1000 person-years in osteoporosis patients with and without bisphosphonate treatment, separately.[12]

Community-based AF incidence varied between countries based on the eight studies.[13-20] For example, annual incidence ranged from 0.05 per 100 person-years to 4.90 per 1000 person-years in the studies from China.[13,15,16] AF incidence in men and women was 7.75 and

8.02 per 1000 person-years with a mean follow-up of 9.16 years, respectively.[14] Annual incidence of AF ranged from 2.07 to 9.30 per 1000 person-years in Japan, [17-19] and was 3.21 per 1000 person-years in one study from South Korea[20].

Community-based AF Prevalence

The lowest AF prevalence reported was 0.03% in India[21] and the highest reported was 3.75% in one study from China[22] with the latter testing a stratified random cluster sampling method.

Within each country, community-based AF prevalence varied from 0.37% to 3.75% in the nine studies from China[4,13,15,16,22-26] and from 0.6% to 2.2% in the four studies from Japan.[27-30] AF prevalence was relatively lower in India, from 0.03% to 0.5% based on three studies.[21,31 32]The prevalence of AF in South Korea[33], Turkey [34] and Malaysia[35] were 1.3%, 1.4% and 0.75%, respectively. The prevalence of AF was similar in South Korea and Turkey. **(Figure 2 and Table 2).** The increasing AF rate in community-based studies with ageing is shown in **e-Figure 3.**"

AF prevalence was usually higher in men than women among the majority studies.[16,22,24,25,29,33] Two papers from Malaysia and a Chinese urban community reported similar AF prevalence between men and women.[23,35] The same article from China showed a lower AF prevalence in men than women in rural community.[23] This proportion remained low throughout the study period with no trends for an increase even in recent years

(**e-Figure 4**).[16,22-25,29,33,35] AF prevalence increased with age in most studies,[15-17,22,25,29,33,35-37] except for one paper from China reporting no association between increased age and AF prevalence in rural community[23] **(Table 2).**

Multiple risk factors such as hyperuricemia,[13,37] lack of regular activity[4,23], alaninetransaminase,[33] and adiponectin level[33] all influenced the prevalence of AF, in additional to traditional factors, such as social demographic factors (age,[4,15,16,23,33] gender,[28,33] body mass index[33]), history of stroke[23], decreased renal function,[30,33] and cardiac factors[23,28] (rheumatic valvular diseases,[24] myocardial infarction,[4,16,24,33] left ventricular hypertrophy,[24] low left ventricular ejection fraction),[4] obesity,[24] alcohol consumption,[24] hypertension (HPT),[16] diabetes mellitus (DM)[4,28] and abnormal cholesterol[23,28].

Hospital-based AF Prevalence

AF prevalence in hospital-based studies was divided into two parts according to whether the report was in association with specific diseases. The general hospital-based prevalence of AF was reported in Japan (15.8%)[38], Qatar (9.2%),[39] and Bahrain (3.4%)[40] respectively. Hospital-based AF prevalence was also higher in men than women in Japan (M:18.4% vs. W:11.7% and M:15.8% vs. W:8.8%). [41,42] In specific diseases as stroke (South Korea: M 15.9% vs. W 22.4%) and chronic obstructive pulmonary disease (COPD) (China: M 2.8% vs. W 5.2%), AF prevalence was lower in men than in women based on studies from South Korea[43] and China.[44]

No reports were found on general hospital-based AF prevalence in Chinese cohorts, five studies on specific diseases, such as stable angina pectoris, chronic kidney disease (CKD), COPD, HPT combined with DM, and IS, associated AF prevalence were published.[44-48] Three studies from middle eastern countries report AF prevalence associated with acute coronary syndrome (ACS, 2.7%),[49] acute myocardial infarction(AMI,1.8%)[50] and acute heart failure (AHF,12%),[51] respectively. The first three common diseases associated with AF were stroke (18.6% in Korea),[43] CKD (14.2% in China)[47] and AHF (12% in seven Middle Eastern countries including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen)[51] **(Figure 3 and e- Table 1).** One hospital-based study reported that smoking was associated with AF prevalence.[41]

Incidence and prevalence of IS in AF

The pooled hospital-based incidence of IS in AF patients was 7.04(6.76-7.33, I^2=0.0%) per 100 person-years based on two papers from China,[52,53] excluding the paper reporting only TE.[54] The annual risk of IS in AF from community-based studies was 1.90%(-0.36%-4.17%, I^2=99.9%, N=5).[29,55-58] Annual IS risk in patients without antithrombotic was 4.9% in the community report from Taiwan.[59]

Annual IS in AF without anticoagulants was 13.3 per 1000 person-years from one paper with mixed community- and hospital-based studies in Japan.[60] When meta-analysis was performed based on hospital- and community- based studies, the IS annual risk in AF was 3.0% (1.06%-4.95%,I^2=99.8%,N=8), [29,52,53,55-58,60]excluding the one paper with duplicate data

in Taiwan[59] **(e- Figure 2 and e-Table 2-3).** No publication bias was seen based on Begg's test. (p=0.25).

Hospital-based IS prevalence in AF ranged 9.5% to 28.3% in studies from Chinese and Korean, [52,54,61-63] with one study data from an Emergency department, of 18.8%.[53] No separate data on IS could be extracted from the paper with TE prevalence of 15.3% in Turkey.[64] IS prevalence in AF is 0.49% (Arab) and 0.36% (south Asian) in hospital studies from Qatar.[65] Only two studies reported community-based IS prevalence in AF from China, ranging 1.9% to 6.0%[16,25] **(e- Table 2-5).**

Use of Antithrombotic Therapy

The use of warfarin in community-based studies from Chinese cohorts was very low, ranging 1.0%-4.1%,[16,25,55] while those from Japan was relatively high, ranging between 49.1%-70.0%.[57,58]In Korea, rate of warfarin use kept stable, ranging 31.96% to 37.4% between 2001 and 2014.[66] The rate of antiplatelet drugs use ranged widely within China (4.8-32.3%),[16,25,55]while similar within Japan (29.3-32.1%) in community-based studies. [57,58]

In Chinese cohorts, 8 hospital-based studies reported on warfarin anticoagulation, ranging from 9.4% to 33.3%[52-54,61,62,67-69]; however, therapy persistence was only 57.9% in those on oral anticoagulants (OAC) treatment during 1-year follow-up.[53] In Turkey and Middle Eastern countries, the percentage of patients with warfarin treatment was less than 50% in hospital-based study.[64,65] The use of antiplatelet drugs (mainly aspirin) in hospital-based

studies accounted for nearly half of AF patients, ranging 40.4% to 67.6%, whether in China, Turkey and Middle Eastern Countries.[52-54,61,62,64,65,69,70] Five hospital-based studies reported the use of non-vitamin K antagonist oral anticoagulants (NOAC) in AF, ranging 0.6% to 6.5%[58,61,62,69,70] **(e- Table 6).**

Discussion

This updated systematic review found an incidence of AF in Asian countries of 5.38 per 1000 person-year, after meta-analyzing 10 studies from 3 countries. Second, the variability was apparent in annual IS rate in AF patients between hospital- and community-based studies (7.04% vs. 1.90%). Third, the annual IS risk in AF patients with oral anticoagulants was lower than those without anticoagulation. However, reported rate of warfarin use was less than 50% in hospital from Asian countries.

Most of the included studies assessed AF incidence and prevalence during the time period from the mid-2000s to mid-2010s. The overall and community-based incidence of new-onset AF in Asian countries was 5.38 and 4.70 per 1000 person-year, respectively, which increased greatly compared with data extracted from the previous systematic review including studies from 1990 to the mid-2000s.[1] We partially ascribed this higher AF incidence to increasing age among Asian populations,[71] which is also consistent with a progressive increase in the worldwide prevalence and incidence of AF.[71] Though this could be confirmed in most included studies, which demonstrated increased AF prevalence with age (e- Figure 3), a large

population based prevalence study with adequate follow up duration is still needed in Asia. Furthermore, the community-based AF prevalence was broadly similar [0.1% to 4%], but hospital- based AF prevalence was a little higher [2.8% to 14%] when compared to that reported in prior analysis.[1]

The community-based AF prevalence also varied widely among Asian countries (ranging 0.03% to 3.75%) or even within the same country as China (0.37% to 3.75%)[4,13,15,16,22-26] and Japan (0.6% to 2.2%).[27-30] The AF prevalence in India (0.03% to 0.5%)[21,31,32] and Malaysia (0.75%)[35] was low, partly due to the selected healthy subjects or younger outpatients in the original studies.[21,31,35 32]To truly reflect the community-based AF prevalence, observational studies on populations with broader ages may be needed in India and Malaysia. AF prevalence in South Korea (1.3%), and Turkey (1.4%) were broadly similar to that reported from Europe and North American (1-2%).[72,73]

Although the community-based AF prevalence in China (0.37%-3.56%)[4,13,15,16,22-26] was relatively high, prevalent oral anticoagulant use (1.0%-4.6%)[16,25,55] was lower compared with other Asian countries. This prevalence was generally higher compared with older data (0.5%-2.7%).[74,75] There was low persistence of OAC use (57.9%) after prescription in hospital,[53] which ranged from 9.4% to 33.3 %.[52-54,61,62,67-69] Data on NOAC use in AF was generally limited although they have been introduced into clinical practice for more than five years,[76] especially in the community-based studies from Asia. Hospital-based papers in China reported a low use of NOACs, ranging from 0.6 % to 6.5%.[58,61,62,69,70] Unsurprisingly,

community-based IS rates associated with AF were higher in Chinese cohorts compared to other Asian countries after meta-analysis (3.1% vs. 1.9%).

Stroke risk related to AF is usually reduced by approximately 64% with the use of OACs (eg. warfarin), and a further 19% reduction could be obtained with NOACs compared to warfarin.[77] Unfortunately, the proportion of NOAC use was low throughout the study period in Asian countries and no trend showing an increase was seen, even in more recent years. Asians also tend to have a higher risk of haemorrhagic stroke compared to non-Asians, especially when on warfarin. In one recent US study, warfarin use with TTR ≥55% was associated with a 77% lower risk of stroke/SE compared to no antithrombotic therapy[78]; however, information on TTR and outcomes in the Asian studies we reviewed were limited.

One different result from prior studies was the inconsistent AF prevalence between men and women, when studies were categorized into urban and rural settings. AF prevalence was higher in women in Chinese rural regions than men, while similar in Chinese urban regions[23] and Malaysia.[35] The study by Wong et at[35] focused on a specific population of patients with hypertension, while the study by Chei et al.[23] mainly focused on elderly populations. Therefore, it would be difficult to draw any definitive conclusions due to baseline differences among studies which may account for the differences in AF prevalence between men and women in urban and rural settings. Other associated comorbidities, such as hyperuricemia and alcohol drinking have been highlighted, in addition to more traditional risk factors.[13,37]

Limitations

Unsurprisingly, interpretation of the collected data would be difficult, since each study is heterogeneous: variability of incidence/prevalence of AF in Asian countries may be mainly due to differences in age distribution and diagnostic strategies between developed and developing countries.

The incidence and prevalence of events (both AF and IS in AF) were generally lower in community-based studies, and underestimation may be a possibility, especially since asymptomatic AF is often neglected by the patients and paroxysmal AF could be missed with 'one off' ECG recordings that were commonly used in most studies.[4,16,21-25,27-30,33,35]. Also, we were unable to draw any conclusions on AF incidence and risk factors such as obesity and uncontrolled hypertension, due to lack of detail in the published papers reviewed.

Furthermore, heterogeneity was evident in meta-analysis of event rates, which was mainly caused by the variation in studied regions, mean ages, representative populations ethnic differences, and the various detection method, including - for example - health insurance claims[14], AF on ECG during a follow up visit[16,17,19] or during inpatient hospitalization[15], ICD-9 Code indicating AF at >2 outpatient visits or 1 inpatient visit[20], Holter monitoring[11], and no details on AF event capture provided[13]. However, the outcomes of the included studies are broadly consistent which has reduces the risk of bias.[79] In our previous review, this potential marked heterogeneity has been acknowledged and hence, our result was not presented after a meta-analysis. Despite these limitations, our findings provide a detailed summary and comparison for AF and its associated IS epidemiology in Asia, which may play a role in

healthcare policy and decision making in developing countries.

Conclusions

AF incidence and prevalence has increased in recent years, though great variability still exists in Asian countries. Variability in annual IS risk in AF patients was evident between hospital- and community-based studies. However, the rate of warfarin use was less than 50% in hospital studies from Asian countries.

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Guarantor statement: GYHL takes responsibility for the content of the manuscript, including the data and analysis.

Author contributions: YB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; YLW, AS, and GYHL contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Conflict of interest: GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, BoehringerIngelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, BoehringerIngelheim, Microlife, Roche and Daiichi-Sankyo. No personal fees received. Other authors: None declared

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Figure Legends

Figure 1 PRISMA flow diagram of Selection Process.

AF, atrial fibrillation; IS, ischemic stroke; N, number.

Figure 2 AF prevalence in community-based studies.

AF, atrial fibrillation.

Figure 3 AF prevalence in hospital-based studies.

AF, atrial fibrillation; Middle Eastern countries refer to 6 adjacent Arabian Gulf countries (Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates and Yemen) in Hersi et al.; Qatar in Salam et al.; seven countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) in Sulaiman et al. and Bahrain in Garadah et al.

Table 1 Characteristics of the studies on incidence of AF in Asian countries

Author	Data source	Period	Study Size	Age(mean/median), y	AF, N	P-y	eFollow-up,year
Chuang,2014[14]	Elderly NAHSIT, Taiwan	1999-2000	1485	72.0	90	11,413	9.16
Chao,2013[13]	NHIRD, Taiwan	2000- 2009	122,524	50.6	2,339	771,901	6.3
Li,2015[16]	CDDMEP, China	2006-2011	3922	NA	34	6,939	3.8
Guo,2015[15]	Medical insurance database, Yunnan, China	2001-2012	471,446	62	921	1,924,975	1.9
Iguchi,2010[17]	Kurashiki Public Health Center, Japan	2006-2007	30,449	73	278	29,893	NA
Watanabe,2011[19]	Niigata, Japan	NA	28,449	59	265	4,042	4.5
Suzuki,2013[11]	Shinken Database, Japan	2004-2010	2,589	54.2	38	4,043	1.57
Sano,2014[18]	CIRCS, Japan	1991-1995	7,206	56.0	296	45,790	6.4
Kang,2016[20]	National insurance program, Korea	2003-2004	132,063	52.6	3,237	1,008,411	9.0
Rhee,2012[12]	Korean-HIRA, Korea	2005-2006	130,182	72.95(B) 72.64(O)	626(B) 66(O)	5,773.4(B) 70,025(O)	NA

NAHSIT, Nutrition and Health Survey in Taiwan; NHIRD, National Health Insurance Research Database;
CDDMEP: the Chronic Disease Detection and Management in the Elderly (⩾60 years) Program;
CIRCS, the Circulatory Risk in Communities Study; HIRA, Health Insurance Review and Assessment;

NA, not available; N, number; B, Bisphosphonate; O, other osteoporosis medication; eFollow-up, estimated follow-up; p-y, person-year; y, year;

d, days.

Table 2 Baseline characteristics of included studies on community-based AF prevalence in Asian countries

Author, year	Period	Data source	Detection method	Age,(mean /median), y	Male (%)	Study Size	AF, N	AF prevalence (%)	Subgroup AF prevalence
Lu, 2012[25]	Apr,2009-Jun,2010	Xinjiang Kazaks, China	Case history; ECG; Physical examination	NA	44.01	22,514	83	0.37%; M:0.59%； W:0.2%	Increase with age
Chao, 2013[13]	2000-2009	NHRID, Taiwan	NA	50.6	73.7	122,524	2,339	1.9%	Hyperuricemia:2.1%; No hyperuricemia:1.7%
Li, 2013[24]	2004	Urban and rural, China	Case history; Current ECG; Both	NA	44.6	19,363	199	0.77%*; M: 0.78%#; W: 0.76%#.	Urban :0.91%; Rural:0.67%; Increase with Age
Chei, 2015[23]	1998-2012	CLHLS, China	Lead-I ECG	85.6	45.5	1,418	50	3.5%; M:2.4%; W:4.6%;	Rural:4.6%;(M<W) No increase with age; Urban:2.3%.(M=W) Increase with Age
Guo,2015[15]	2001-2012	Yun nan ,China	NA	62	62	471,446	1,237	0.2%	Increase with age
Li, 2015[16]	2006-2011	CDDMEP, China	12-lead ECG	NA	43.8	3,922	70	1.8%; M：2.0%;W：1.6%	Increase with age Men> women

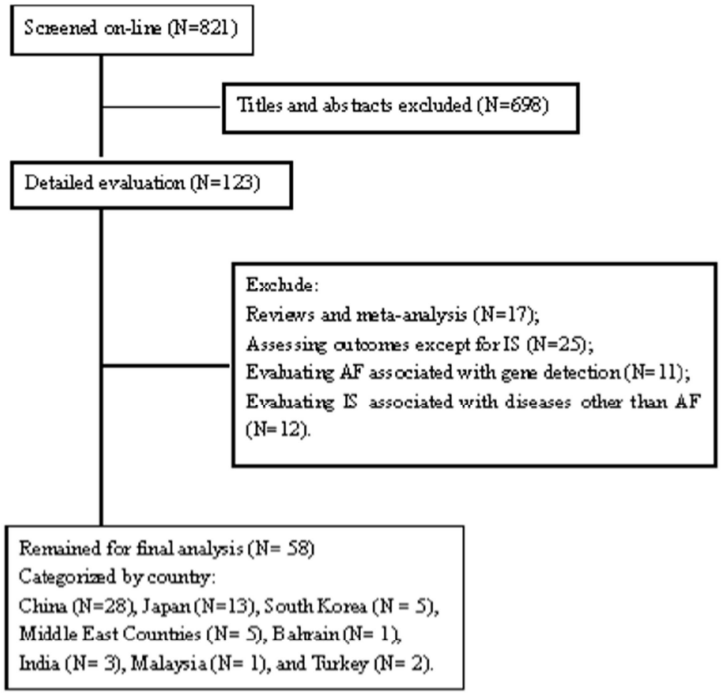
Sun, 2015[4]	Jan-Aug, 2013	rural Liaoning, China	self-reported; ECG; Both	NA	45.6	11,956	139	1.20%	Hyperuricemia:2.4%; No hyperuricemia:1.0% Increase with age
Miao, 2015[22]	NA	Xinjiang, China	12-lead ECG UCG	Uygur: 68.68 Han: 68.11	49.3	5,398	192	Crude:3.56%; Stand :3.75%; Han: M:5.01%; W:3.31%; Uygur: M:3.19%;W:2.61%	Increase with age
Modesti, 2016[26]	2014	CHIP	Single channel ECG	41.7	44.4	1,608	12	0.74%	Increase with age
Hingorani, 2012[21]	2005-2009	Healthy volunteers, India	12-lead ECG	31	62.7	3,978	1	0.025%	NA
Kalra, 2015[31]	Jan,2011-Feb,2014	PIQIP, India	NA	50.6	69.9	68,196	348	0.5%; M:0.34% W:0.87%	NA
Saggu,	NA	Urban, Nagpur,	12-lead ECG	43.9	55.5	4,077	8	0.196%	Increase with age

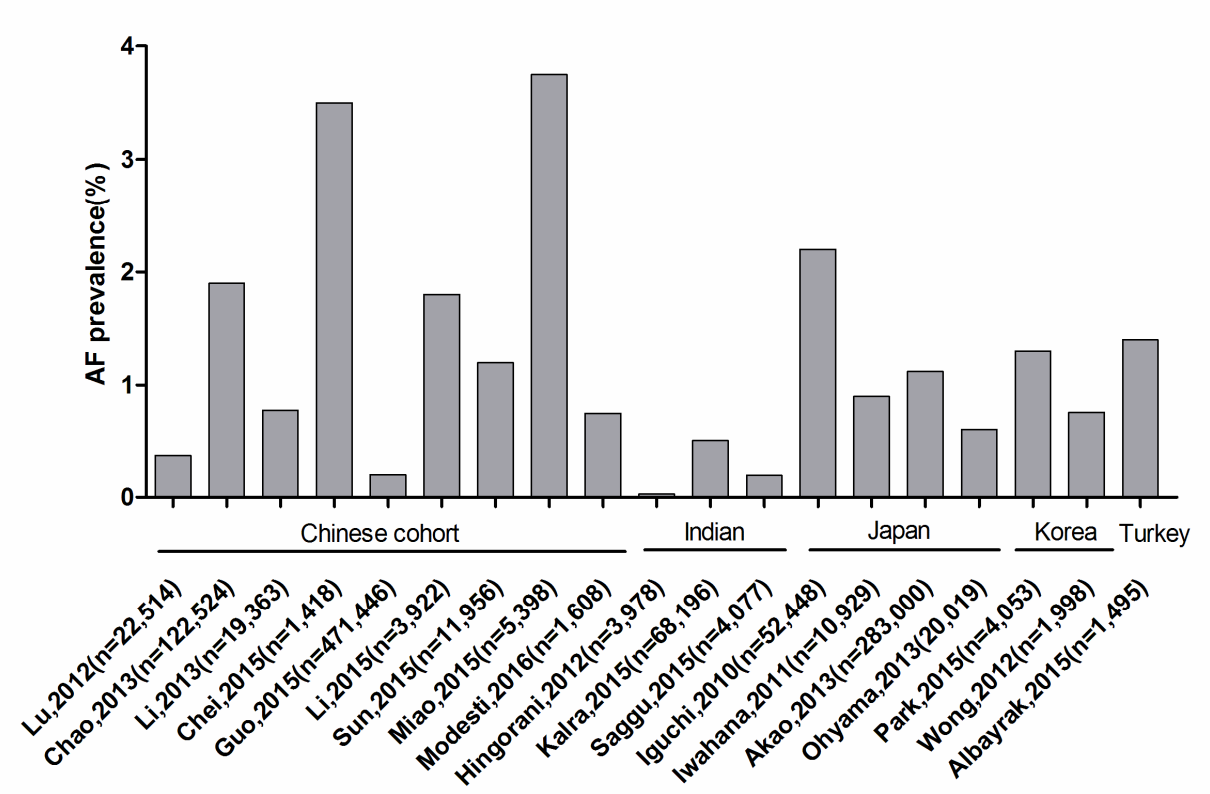
2015[32]		India							
Iguchi, 2010[28]	2006-2007	KAMS, Japan	12-lead ECG	72	34.3	52,448	1161	2.20%	Increase with age
Iwahana, 2011[29]	Apr,1992-Jul,1995	JMS, Japan	12-lead ECG; Physical examination	NA	37.9	10,929	54	AF: 54(0.9%) M: 30 (0.72%) W: 24 (0.35%)	Increase with age Men > women
Akao, 2013[27]	Mar,2011-Jun, 2012	Fushimi-ku, Japan	12-lead ECG; Holter	74.2	59.3	283,000	3183	1.12%	Young: paroxysmal; Older: persistent / permanent
Ohyama, 2013[30]	Apr,2011-Mar,2012	Gunma, Japan	12-lead ECG	53.2	62	20,019	112	0.60%	Increase with lower renal function
Park, 2015[33]	Jan,2005-Dec,2009	Yangpyeong, Korea,	12-lead ECG	60.2	38.9	4,053	54	1.3%; M:2.0%; W: 0.9%. 0.36%#; M: 0.45%#;W: 0.32%#.	Increase with age M > W
Wong, 2012[35]	Aug -Oct, 2011	Bumiputera Sarawak:78.2%;	Home-health records;	M: 55 W: 51	38.4	1,998	15	0.75%	Increase with age M=W

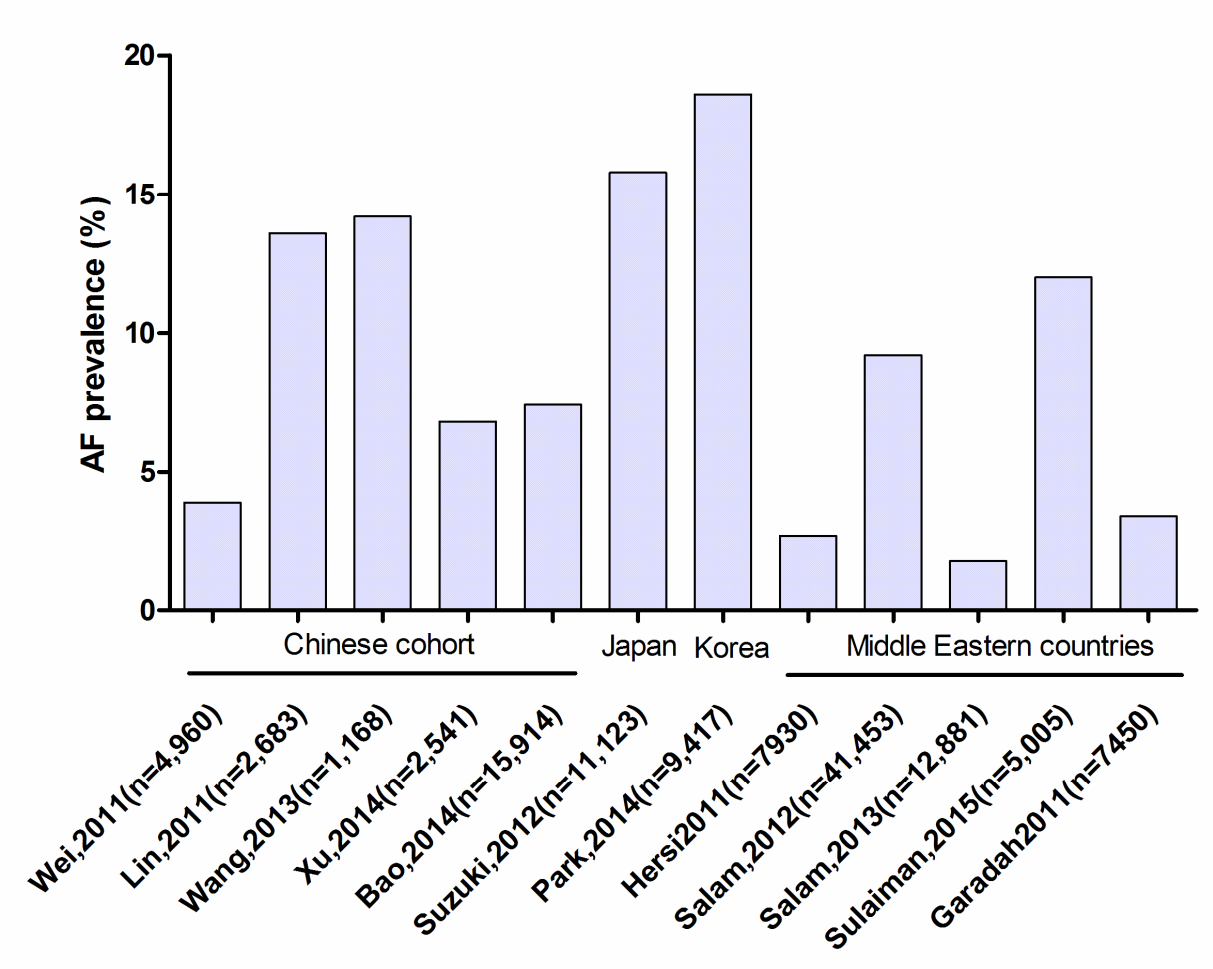
		Malay/Melanau: 12.8%; Chinese:9%.	12-lead ECG						
Albayrak, 2015[34]	NA	MELEN study , Turkey	NA	NA	38.1	1,495	21	1.4%	NA

NHIRD, National Health Insurance Research Database; CLHLS, the Chinese Longitudinal Healthy Longevity Survey; CDDMEP: the Chronic Disease Detection and Management in the Elderly (≥60 years) Program; PIQIP, Practice Innovation and Clinical Excellence (PINNACLE) India Quality Improvement Program; KAMS, Kurashiki-city Annual Medical Survey; JMS, The Jichi Medical School; CHIP, Chinese in Prato. GRED, gastroesophageal reflux disease; HPT, hypertension;

*, age-sex-adjusted AF prevalence; # Age-adjusted AF prevalence; C, Community;.






AF prevalence (%)
20
15
10
5
0
Chinese cohort
Japan
Korea
Middle Eastern countries
Wei,2011(n=4,960)
Lin,2011(n=2,683)
Wang,2013(n=1,168)
Xu,2014(n=2,541)
Bao,2014(n=15,914)
Suzuki,2012(n=11,123)
Park,2014(n=9,417)
Hersi2011(n=7930)
Salam,2012(n=41,453)
Salam,2013(n=12,881)
Sulaiman,2015(n=5,005)
Garadah2011(n=7450)

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e-Table 1. Baseline Characteristics of studies on hospital-based AF prevalence in Asian countries

Author, year	Associated disease	Period	Data source	Study size	Male (%)	Age(mean or median), y	AF, N	AF prevalence, (%)
Wei, 2011[27]	COPD	Jan,2000-Mar,2010	PLA General Hospital, Beijing Xiehe Hospital, Beijing Hospital, China	4,960	72	72.2	196	3.9 M: 2.8; W: 5.2.
Lin, 2011[28]	First IS	Mar,2002-Dec,2008	Department of Neurology, West China Hospital, Sichuan University, China	2,683	58.4	AF:66.1; No-AF: 63.58.	366 NVAF:213 VAF:153	13.6 NVAF:7.9 VAF:5.7
Wang, 2013[29]	CKD	Jan,2006-Jun,2011	Tertiary level Hospital, Chongqing, China	1,168	54.5	63.3	166	14.2
Xu, 2014[30]	Stable AS	Jan-Dec,2011	Fuwai Hospital, China	2,541	69.5	AF:68.6; No AF:59.3	173	6.8
Bao, 2014[31]	HPT+DM	Oct,2011-Jun, 2012	36 Tertiary Hospital, China	15,914	49.7	64.6	1,174	7.4
Suzuki, 2012[32]	NA	2004-2008	Shinken Database, Japan	11,123	61.7	M: 57.1; W: 60.7.	1,131 M:811 W:320	15.8 M:18.4 W:11.7
Suzuki, 2013[33]	NA	2004-2011	Shinken Database, Japan	M:10,714 W:6,803	61.2	AF: M: 61.4; W: 69.3. No AF: M: 58.1; W: 55.7.	M:1,698; W:598	M:15.80 W:8.8

Park, 2014[34]	stroke	Apr,2008-Jan,2011	CRCS, Korea	9,417 (M:5,459; W:3,958)	58	M: 64.8; W: 71.2.	M:867; W:888	18.6 M:15.9; W:22.4
Hersi, 2011[35]	ACS	Oct,2008-Jun, 2009	Gulf RACE-2 registry, Middle Eastern countries	7,930	78.7	56.8	217	2.7
Salam, 2012[36]	NA	1991-2010	Middle Eastern countries	41,453	NA	NA	3,848	9.2
Salam, 2013[37]	AMI	1991-2010	Middle Eastern countries	12,881	NA	Arab: 58; Asian: 49.	227	1.8
Sulaiman, 2015[38]	AHF	Feb-Nov,2012	Gulf CARE, Middle Eastern countries	5,005	62.6	59;	607	12
Garadah, 2011[39]	NA	Jan-Dec,2010	ER, (Bahrain) Middle Eastern countries	7,450	NA	NA	253	3.4

Gulf CARE, Gulf aCuteheArt failuRe rEgistry; Gulf RACE-2 registry, the second Gulf Registry of Acute Coronary Events(including Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates [UAE], and Yemen); ER, acute medical emergencies; CRCS, the Clinical Research Center for Stroke project; *, including Atrial Fibrillation and Atrial flutter; AMI, acute myocardial infarction; AHF, acute heart failure; AS, angina pectoris; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases; HBP+DM, hypertension and diabetes mellitus; IS, ischemic stroke; ACS, acute coronary syndrome; NA, not available; M, men; W, women; N, number.

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e-Table 2. Baseline characteristics of studies on incidence of Hospital-based ischemic stroke in Asian countries

Author, year	Period	Data source	Study size	Male (%)	Age(Mean/ median) , y	Follow-up	IS, N(%)
Yang, 2014[40]	Nov,2008-Oct,2011	EDs in 20 hospitals in China	2,016*	45.2	64.5	1-y	148(7.4%)
Siu, 2014[41]	Jul,1997-Dec, 2011	Queen Mary Hospital, Hong Kong	9,727	47.9	76.9	3.19y	2,179(22.4%)
Suzuki, 2015[42]#	Shinken:2004-2012; J-RHYTHM: Jan -July 2010; Fushimi: Mar,2011-	Shinken Database (N=1099), J-RHYTHM Registry(n=1002), Fushimi AF Registry (n=1487) Without anticoagulants	3,588	66.1	68.1	1.4 y	69

NHIRD, National Health Insurance research database in Taiwan; J-TRACE, the Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events; J-RHYTHM, Investigation of optimal anticoagulation strategy for stroke prevention in Japanese patients with atrial fibrillation; Fushimi AF Registry, The Registry Study of Atrial Fibrillation Patients in Fushimi-ku; AFTER, Atrial Fibrillation in Turkey: Epidemiologic Registry; JMS, The Jichi Medical School cohort study; IS, ischemic stroke; AF, atrial fibrillation; ED, emergency department; N, number. * including atrial fibrillation and atrial flutter; #, with both hospital and community - based studies

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e-Table 3. Baseline characteristics of studies on incidence of community-based ischemic stroke in Asian countries

author, year	Male (%)	Age (Mean/median), y	Period	Data source	Study size	Follow-up	IS, N (percentage, %)
Guo, 2015[43]	62	62	2001-2012	Medical insurance database, Yunnan, China	T:471,446 AF:921	11 y	59
Chang, 2014[44]*	56.7	74.5	Jan, 2002- Dec, 2004	NHIRD in Taiwan	T:22,842,778 AF:24,612	-Dec 31, 2010	5183
Chao, 2014[45]*	54.6	With stroke:73.4; No stroke:69.4	Jan,2000- Dec,2009	NHIRD in Taiwan, No antithrombotic agents	AF:7,601	3.0 ± 2.7 y,	1116 (14.7%)
Goto, 2011[46]	68.7	70	NA	J-TRACE, Japan	AF:2,056	1 y	-0.15%
Iwahana, 2011[21]	55.6	M:64.9; W:66.8.	Apr,1992- Jul,1995	JMS, Japan	T:10,929 AF:54	10.7 y	12
Takabayashi, 2015[47]	PAF:58; SAF:61.	PAF:72.3; SAF:74.9.	Mar,2011- Jul,2014	The Fushimi AF Registry, Japan	AF:3,304 (PAF :1,588; SAF :1,716)	746 d	IS : No OAC: (1.4%); With OAC: (2.0%).

*, the two papers using data from the same dataset.
NHIRD, National Health Insurance research database in Taiwan; J-TRACE, Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events; JMS, The Jichi Medical School Cohort Study; J-RHYTHM, Investigation of optimal anticoagulation strategy for stroke prevention in Japanese patients with atrial fibrillation; Fushimi AF Registry, The Registry Study of Atrial Fibrillation Patients in Fushimi-ku; IS, ischemic stroke; AF, atrial fibrillation.

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e-Table 4. Baseline characteristics of studies on prevalence of hospital-based ischemic stroke in Asian countries

Author, year	Male (%)	Age(mean/median), y	Period	data source	study size	IS (percentage)
Guo, 2014[48]	58.2	64.8	Jan,2008-Dec,2012	12 hospitals in Urumqi, China	1,310	125(9.5%)
Yang, 2014[40]	45.2	64.5	Nov,2008-Oct,2011	20 representative ED, China	2,016*	379(18.8%)
Siu, 2014[41]	47.9	76.9	Jul,1997-Dec, 2011	Queen Mary Hospital, Hong Kong	9,727	2,295 (23.1%)
Guo, 2013[49]	72.9	75	Nov,2007-Jul, 2010	PLA General Hospital, China	1,034	209 (20.2%)
Sun, 2014[50]	60.6	66.6	Dec,2009-Oct,2010	29 Tertiary level Hospital, China	805	116(14.4%)
Cha, 2014[51]	66.3	AF:66.6 No-AF:65.83	Jan,2000-May,2012	Korea	T:1200; AF:400	113(28.3%)
Salam, 2013[52]	NA	Arab:58; Asian:49	1991-2010	Middle Eastern countries	Arab:2857 Asian:548	Arab: 14(0.49%) Asian: 2(0.36%)
Ertaş, 2013[53]	39.8	80.3	NA	AFTER 17 tertiary health care centers, Turkey (inpatient and ED excluded)	2242	IS/TIA/SE:(15.3%)

ED, emergency department; AF, atrial fibrillation; IS, ischemic stroke; AFTER, Atrial Fibrillation in Turkey: Epidemiologic Registry; *, including atrial fibrillation and atrial flutter.

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e-Table 5. Baseline characteristics of studies on prevalence of community-based ischemic stroke in Asian countries

Author, year	Male (%)	Age , y (Mean/median)	Period	Data source	Study size	Antithrombotic therapy	IS, N (%)
Li, 2015[3]	NA	NA	2006-2011	CDDMEP	T:3,922; AF:104	Aspirin, 5 (4.8 %) Warfarin, 1 (1.0 %)	2(1.9%)
Lu, 2012[11]	44.01	NA	Apr,2009- Jun,2010	Xinjiang Kazaks, China	T: 22,514 AF:83	Warfarin, 2(2.4%) Aspirin, 16(19.3%)	-6.00%

NA, not available; CDDMEP: the Chronic Disease Detection and Management in the Elderly (≥60 years) Program; T, total patients; AF, atrial fibrillation; IS, ischemic stroke.

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e-Table 6. Baseline characteristics of studies on OAC use in AF in Asian countries

Author, year	Period	Data source	Study size	No OTA	Antiplatelet	Warfarin or OAC, N (%)	NOACS, N(%)
Chang, 2016[54]	2011-2014	CAFR	7,977			ChA_2DS_2-VASc score: ≥2: (36.5%); 1: (28.5%); 0: (21.4%).	
Xiang, 2015[55]	2012-2013	Peking University First Hospital, China	1,000	-31.40%	-39.50%	-27.80%	-1.30%
Xiong, 2015[56]	2011-2013	Nanchang AF project, China	2,442			Pre-hospital: 173 (7.3%); Hospitalization: 791 (33.3%).	
Zhang, 2016[57]	2012-2015	AFAIS, China	1,014	-22.50%	-57.50%	-9.40%	-0.60%
Guo, 2014[48]	Jan,2008-Dec,2012	12 hospitals in Urumqi, China	1,310*		655 (50.0%)	284 (21.7%)	54 (4.1%)
Yang, 2014[40]	Nov,2008-Oct,2011	20 EDs, China	2,016#	-24.70%	56.70%	**OAC :** (8.6 %)	
			Baseline			**OAC :** (11.8 %)	
			1-y follow-up			**OAC :** (57.9 %)	
Siu, 2014[41]	Jul,1997-Dec, 2011	Queen Mary Hospital, Hong Kong	9,727	-39.90%	40.40%	-19.70%	

Guo, 2013[49]	Nov,2007-Jul, 2010	PLA General Hospital, China	1,034	-18.00%	-67.60%	-14.40%	
Sun, 2014[50]	Dec,2009-Oct,2011	29 Tertiary level Hospital, China	805	-19.80%	-51.60%	-22.20%	-6.50%
Li, 2015[3]	2006-2011	CDDMEP	T:3922; AF: 104		5 of 104 (4.8 %)	1 of 104, (1.0 %)	
Guo, 2015[43]	2001-2012	medical insurance database, Yunnan	T:471,446 AF:921		298 of 921 (32.3%);	38 of 921,(4.1%)	
Lu, 2012[11]	Apr,2009-Jun,2010	Xinjiang Kazaks, China	T:22,514 ; AF:83		16 of 83, (19.3%)	2 of 83, (2.4%)	
Goto, 2011[46]	NA	J-TRACE	2,056		-30.10%	-70.00%	
Takabayashi, 2015[47]	Mar,2011-Jul,2014	The Fushimi AF Registry	3304		-29.30%	-49.10%	
			PAF :1588;		476 (30.0%);	557 (35.0%)	D:51 (3.0%);R:8 (0.5%); Ap:2 (0.1%)
			SAF :1716		492 (29.0%)	1066(62.0%)	D:53 (3.0%);R:13 (0.8%); Ap:1 (0.1%)

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Choi, 2016[58]	2011-2014	HIRA, Korea	113,037			2011(31.9%); 2012 (33.3%); 2013(35.7%); 2014(37.4%).	
Salam, 2013[52]	1991-2010	Qatar Middle eastern country	3,405				
			Before Admission		1,055(31.0%)	56(1.6%)	
			During Admission		1,786(52.5%)	615(18.1%)	
			Discharge		1878(55.2%)	1124(33.0%)	
Ertaş, 2013[53]		17 tertiary health care centers, Turkey	2242*		-60.00%	(37.0%);	

*including non-valvular atrial fibrillation and valvular atrial fibrillation;#including atrial fibrillation and atrial flutter; CAFR, Chinese Atrial Fibrillation Registry; CDDMEP: the Chronic Disease Detection and Management in the Elderly (≥60 years) Program; AFAIS atrial fibrillation-associated ischemic stroke; NHIRD, National Health Insurance research database in Taiwan; J-TRACE, the Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events; J-RHYTHM, Investigation of optimal anticoagulation strategy for stroke prevention in Japanese patients with atrial fibrillation; Fushimi AF Registry, The Registry Study of Atrial Fibrillation Patients in Fushimi-ku; HIRA ,Health Insurance Review and Assessment Service; AFTER ,Atrial Fibrillation in Turkey: Epidemiologic Registry; JMS, The Jichi Medical School cohort study; AFAIS, atrial fibrillation-associated ischemic stroke; ED, emergency department; AF, atrial fibrillation; A, aspirin; W, warfarin; D, dabigatran; R, rivaroxaban; Ap, apixaban; PAF, paroxysmal atrial fibrillation; SAF, persistent atrial fibrillation; OTA, oral antithrombotic agents therapy; OAC, oral anticoagulant agents therapy; NOACs, noval oral anticoagulant agents.

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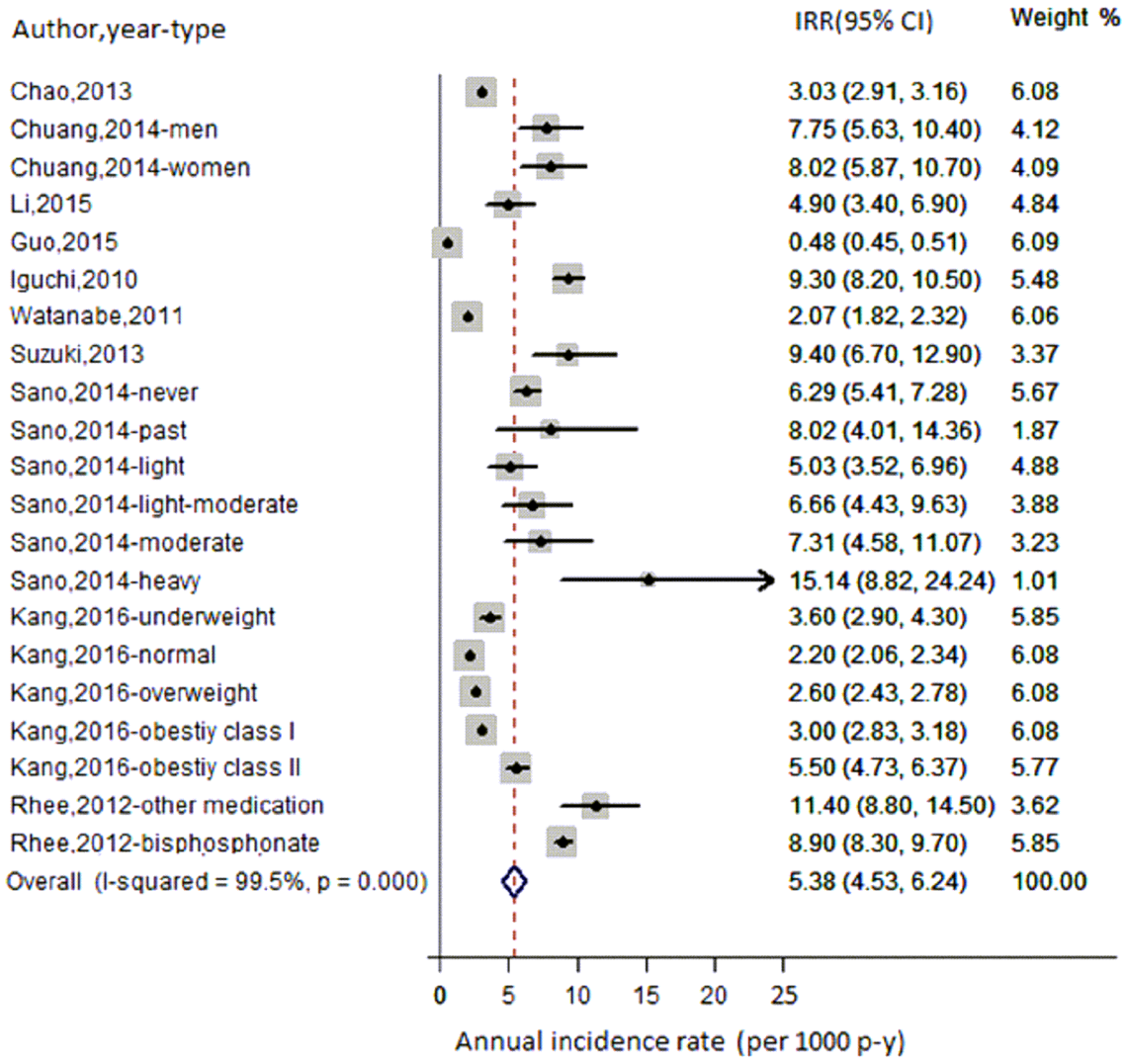

e- Figure 1. Annual incidence of atrial fibrillation in Asian Countries (events/1000 person-years).

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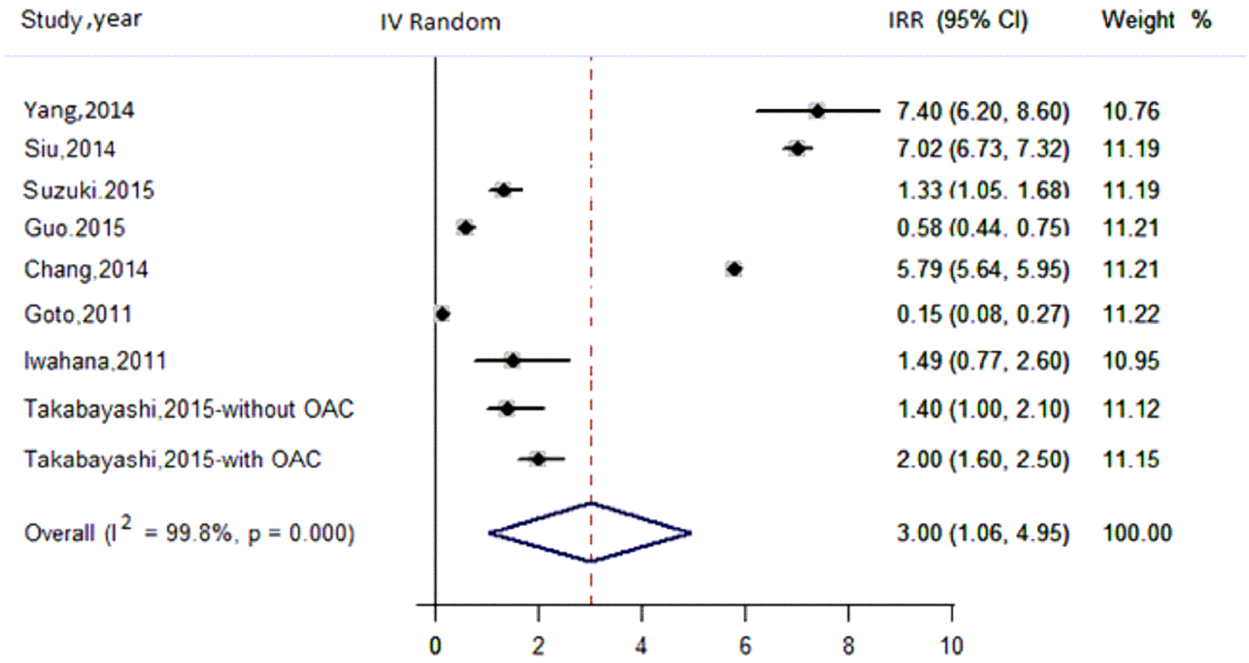

e- Figure 2. Annual rate of ischemic stroke in atrial fibrillation in both community- and hospital-based studies in Asian countries.

OAC, oral anticoagulant agent.

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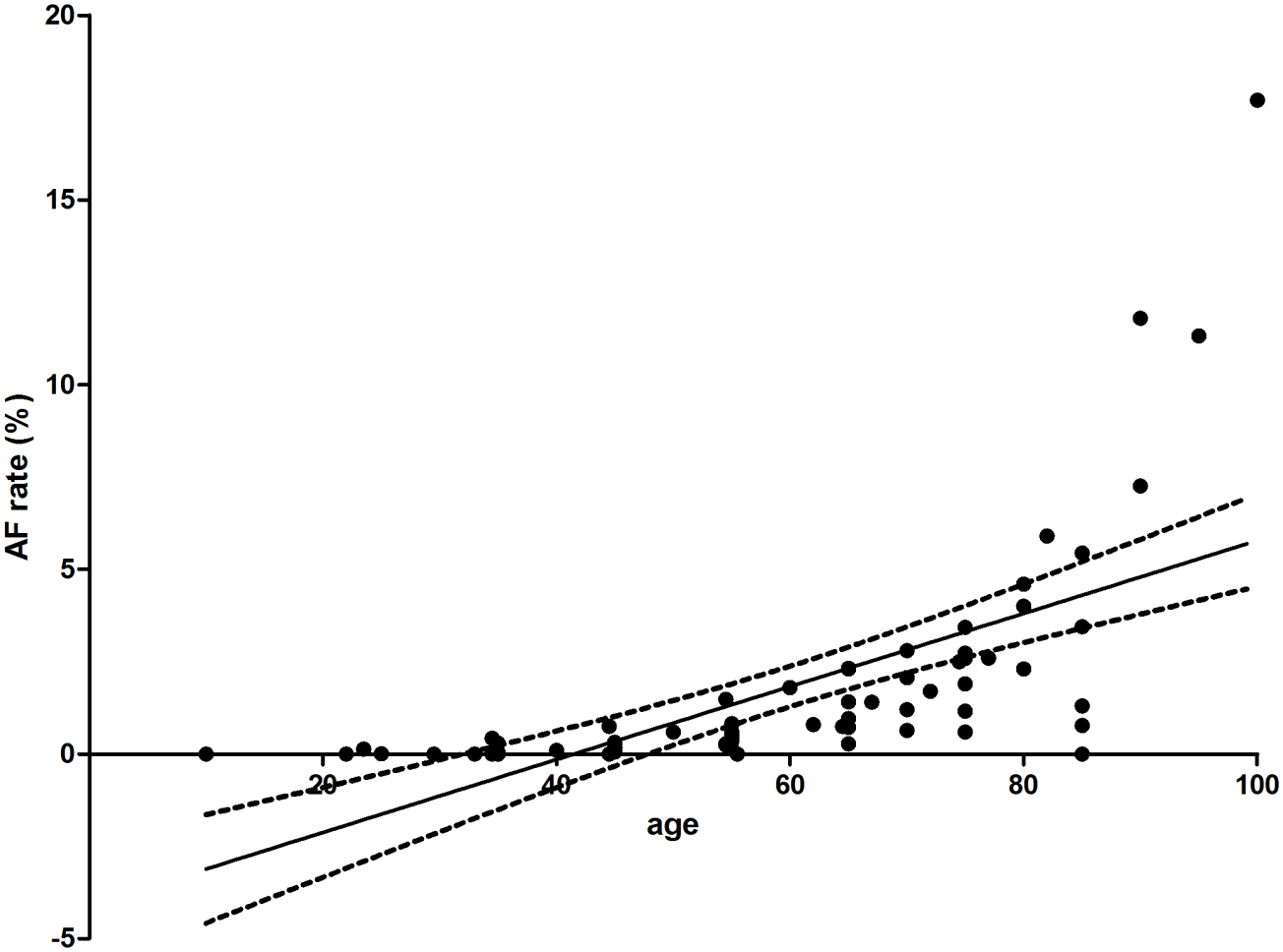

e- Figure 3. Weighted regression of AF rate in community-based studies.

This figure presents community-based AF rate with increasing age. The dashed line indicated 95% CI of the fitted line. The points indicated the separate AF rate with according age. AF, atrial fibrillation; CI, confidence interval.

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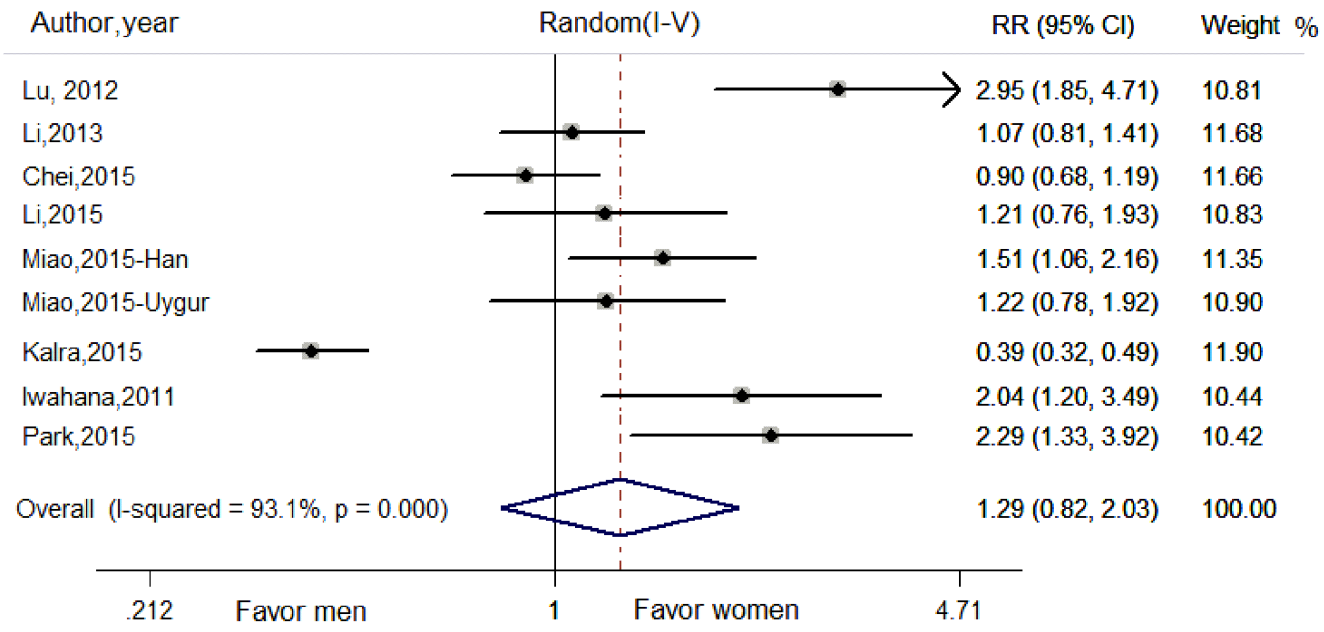

e- Figure 4. Relative Risk of AF incidence between men and women in community-based studies.

AF, atrial fibrillation; CI, confidence interval.

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