



The risk of all-cause death and death from various causes according to prevalent atrial fibrillation : a nationwide population-based study



Young-Kwan Kim (presenter)¹

So-Ryoung Lee¹, Eue-Keun Choi², Hyun-Jin Ahn¹, Nan-Young Bae¹, Kyung-Yeon Lee¹, Jungmin Choi¹, Hyo-Jeong, Ahn¹, Soonil Kwon¹, Kyung-Do Han³, Seil Oh², Gregory Y.H. Lip⁴

¹ Seoul National University Hospital, Republic of Korea

² Seoul National University College of Medicine, Republic of Korea

³ Department of Statistics and Actuarial Science, Soongsil University, Republic of Korea

⁴ Liverpool Centre For Cardiovascular Science At University Of Liverpool, Liverpool John Moores University And Liverpool Chest & Heart Hospital, United Kingdom

Korean Heart Rhythm Society

COI Disclosure

Name of First Author: Young-Kwan Kim

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Epidemiology of AF

Increasing prevalence and lifetime risk due to

- Age
- Burden of other comorbidities (e.g. DM, HF, CAD, CKD, obesity)

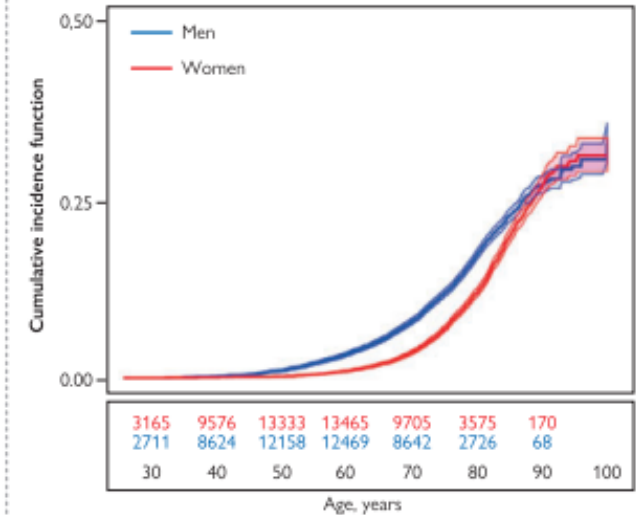
LIFETIME RISK for AF
1 in 3 individuals



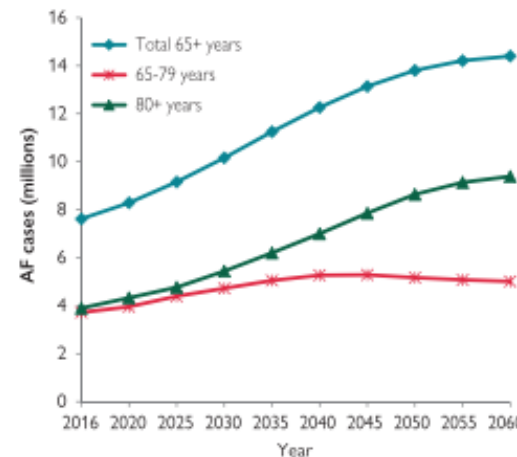
of European ancestry
at index age of 55 years
37.0% (34.3% to 39.6%)

AF is more common in males

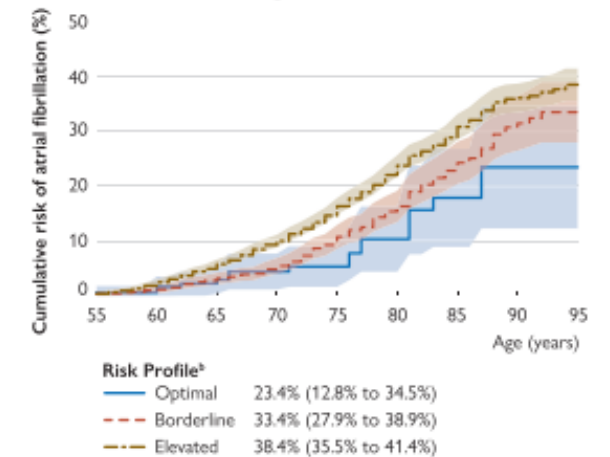
Cumulative incidence curves and 95% CIs for AF in women and men with death as a competing risk



Projected increase in AF prevalence among elderly in EU 2016-2060



Lifetime risk of AF increases with increasing risk factor burden^a



Epidemiology of AF - Korea

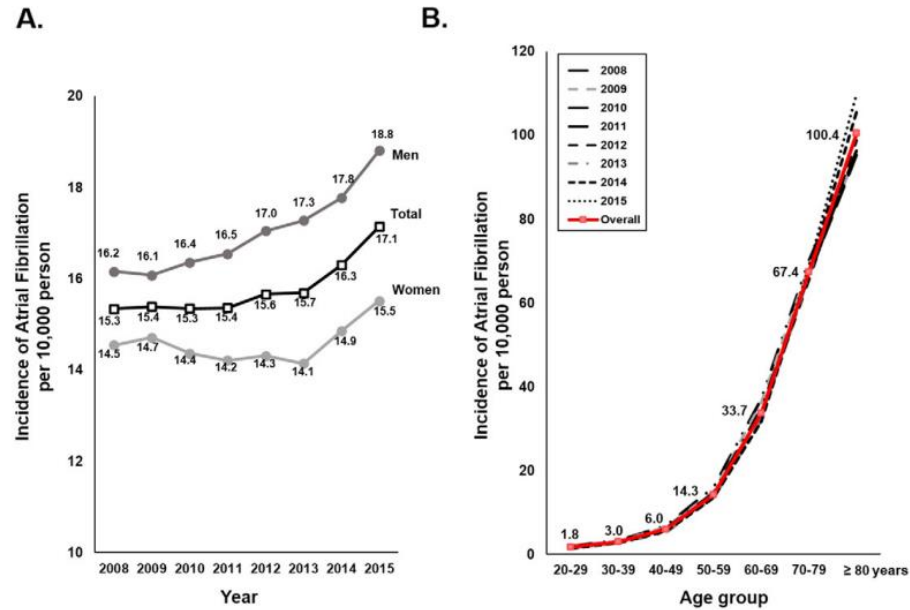


Fig. 1. Incidence of atrial fibrillation between 2008 and 2015 (per 10,000 person-years). A, Annual incidence of atrial fibrillation stratified according to sex. B, Incidence of atrial fibrillation according to age group in each year.

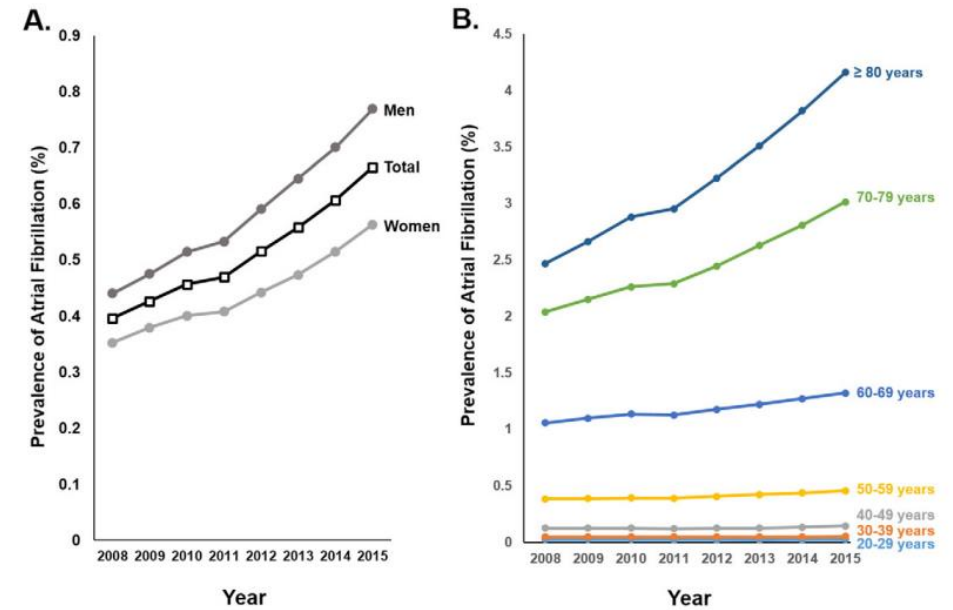


Fig. 2. Prevalence of atrial fibrillation between 2008 and 2015. A, the annual prevalence of atrial fibrillation stratified according to sex. B, Temporal trends of the prevalence of atrial fibrillation according to age group.

Increasing incidence and prevalence of atrial fibrillation annually



Increasing hospitalization & ER visit due to AF

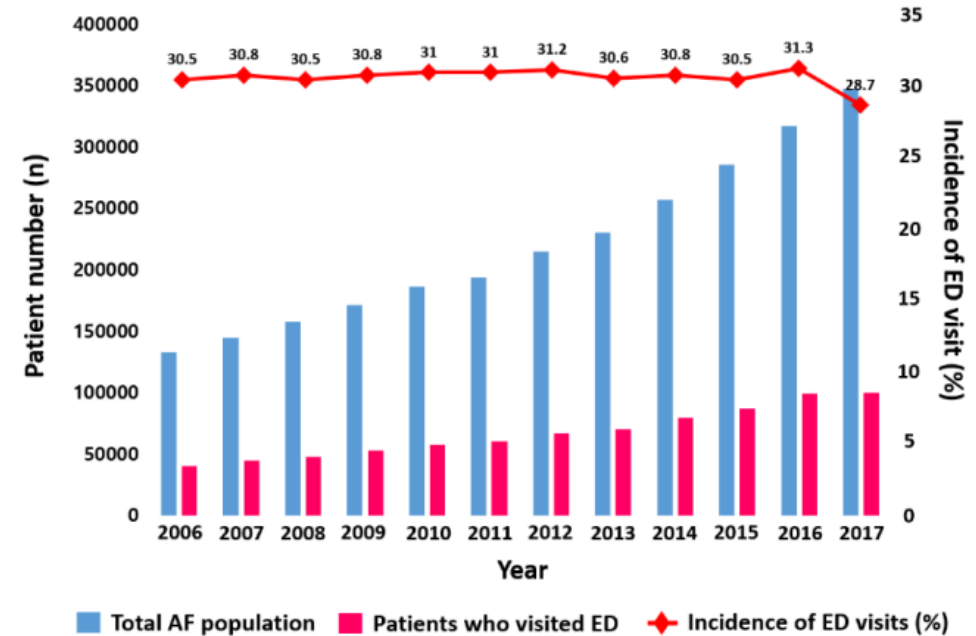
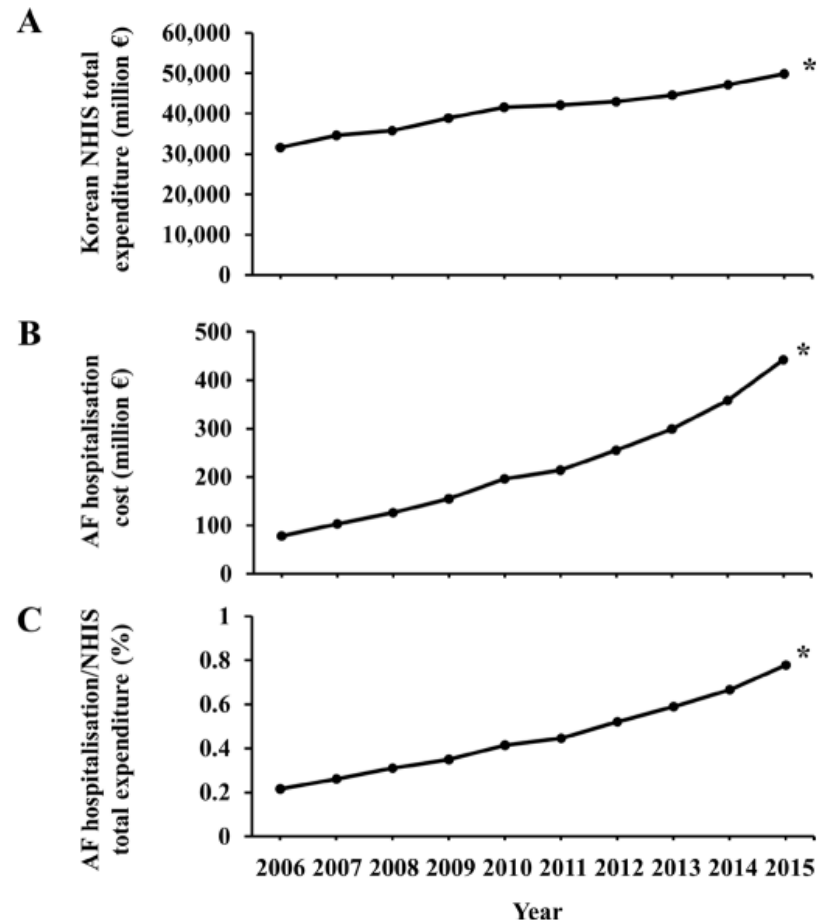


Figure 1. Number of total AF population, patients who visited ED from 2006 to 2017, and incidence of emergency department visits in Korean AF population. Abbreviations: AF, atrial fibrillation; ED, emergency department.

“Uncontrolled Atrial Fibrillation”



Adverse events of AF

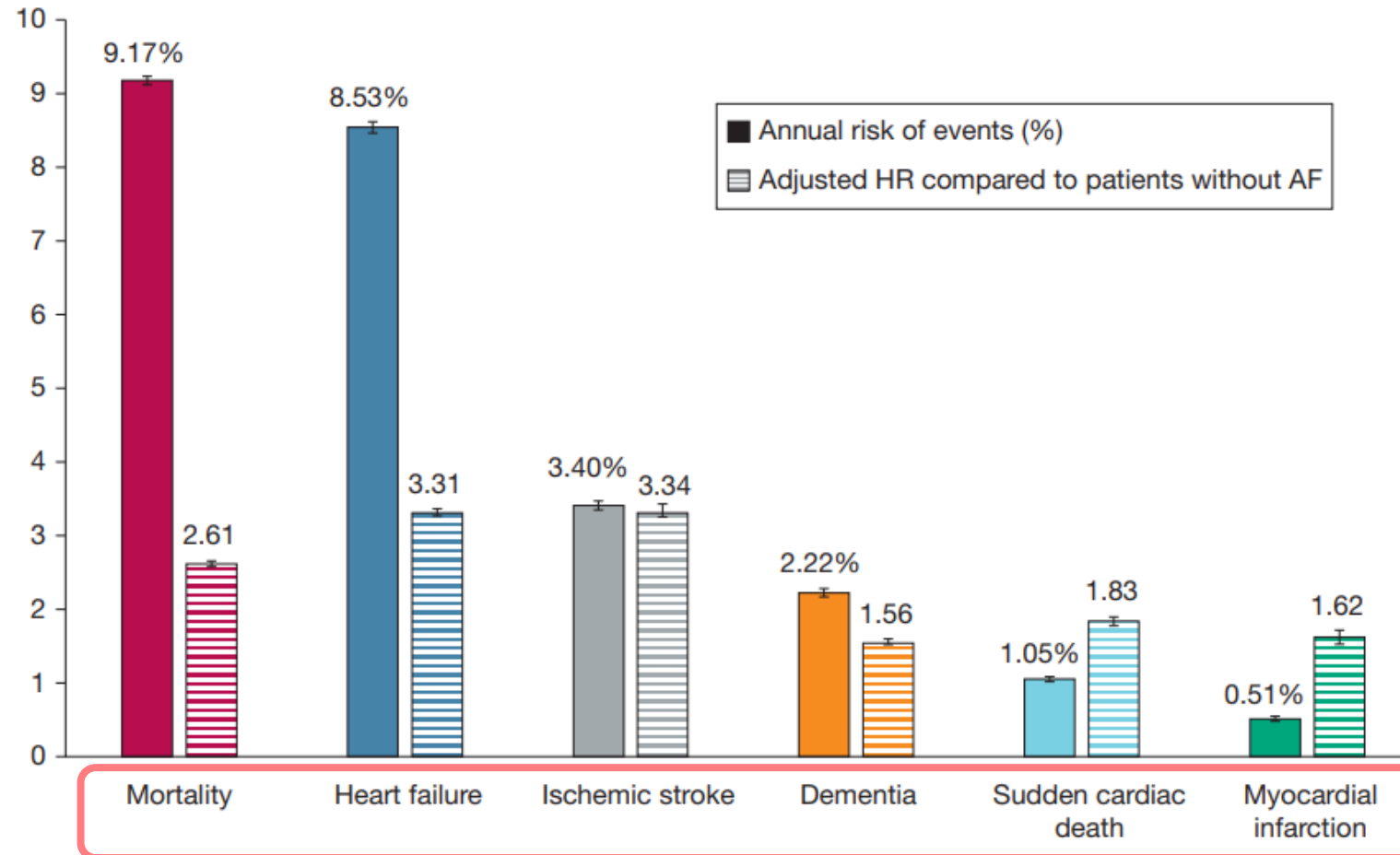


Figure 6 – Annual risks of adverse events of patients with AF and HR compared with patients without AF. This annual risk ranged from 0.51% for myocardial infarction to 9.17% for mortality. Compared with patients without AF, AF was associated with a 1.56-fold to 3.34-fold increase of various events after the adjustment for age, sex, and comorbidities. The risks of different adverse events were investigated among different subpopulations, as discussed in the Methods section. HR = hazard ratio. See Figure 1 legend for expansion of other abbreviation.



Study purpose

Ischemic stroke

Thromboembolism

Heart failure

Myocardial infarction

Dementia

Sudden cardiac death

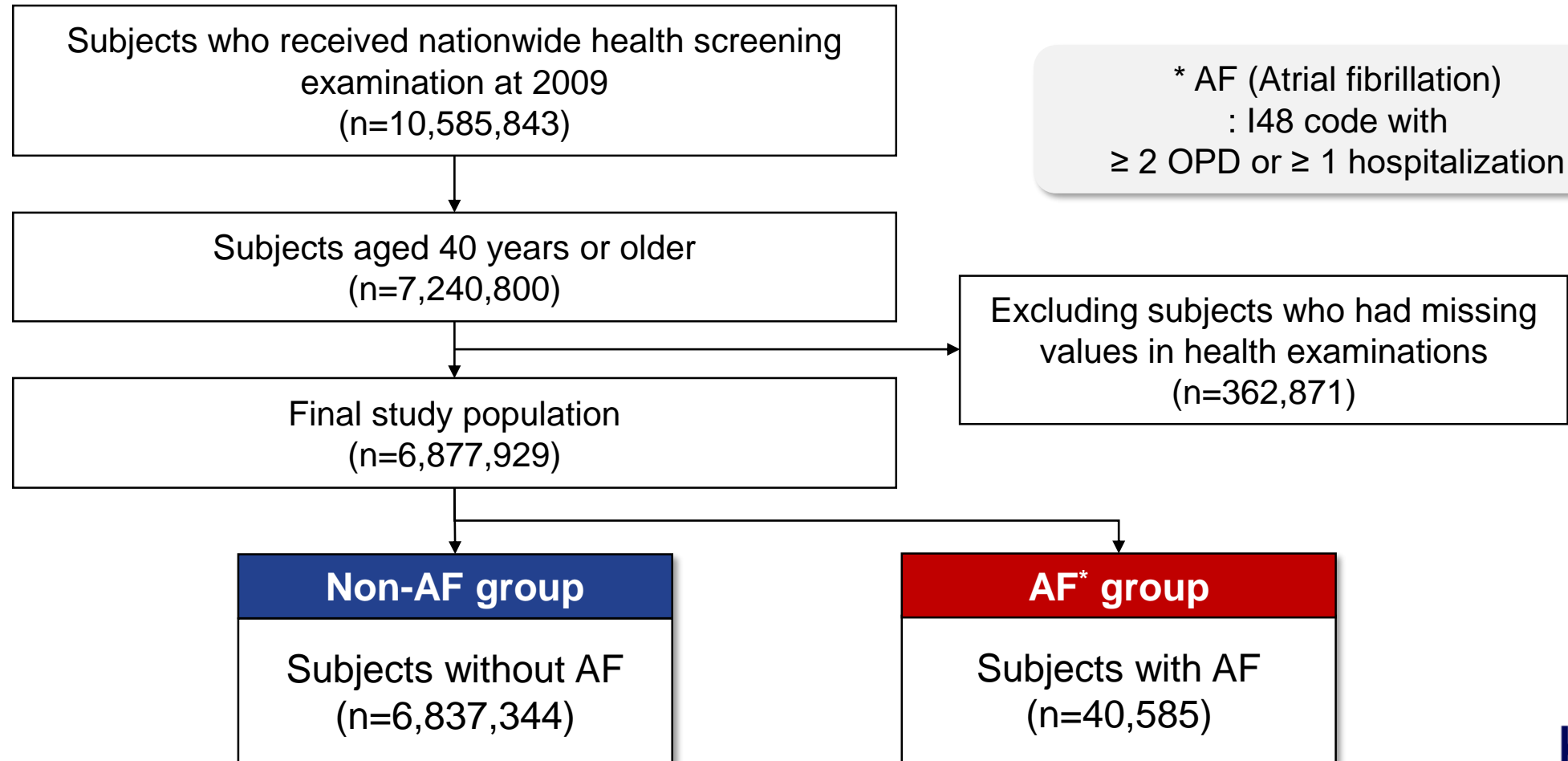
***This study was aimed to investigate
the cause of death (COD) of AF
patients using a nationwide
population-based cohort***



Study Population

Database

National Health Insurance Service (NHIS)



Method – Statistical Analysis

- **Incidence rate (IR)**
 - Number of deaths / total follow-up duration (as 1,000 person-years)
- **Hazard ratio (HR) with 95% confidence interval (95% CI)**
 - Cox proportional regression model
 - Adjustment model
 - *Model 1* : unadjusted
 - *Model 2* : adjusted for age, sex
 - *Model 3* : adjusted for age, sex, smoking status, alcohol consumption level, regular physical activity
 - *Model 4* : adjusted for age, sex, smoking status, alcohol consumption level, regular physical activity, diabetes mellitus, hypertension, dyslipidemia, CKD
 - *Model 5* : adjusted for age, sex, smoking status, alcohol consumption level, regular physical activity, diabetes mellitus, hypertension, dyslipidemia, CKD, cancer history, depression, ischemic heart disease, stroke



Method – Statistical Analysis

- **Follow-up duration**
 - until death or end of study period (December 31st, 2019)



Method – Diagnostic codes of ICD-10

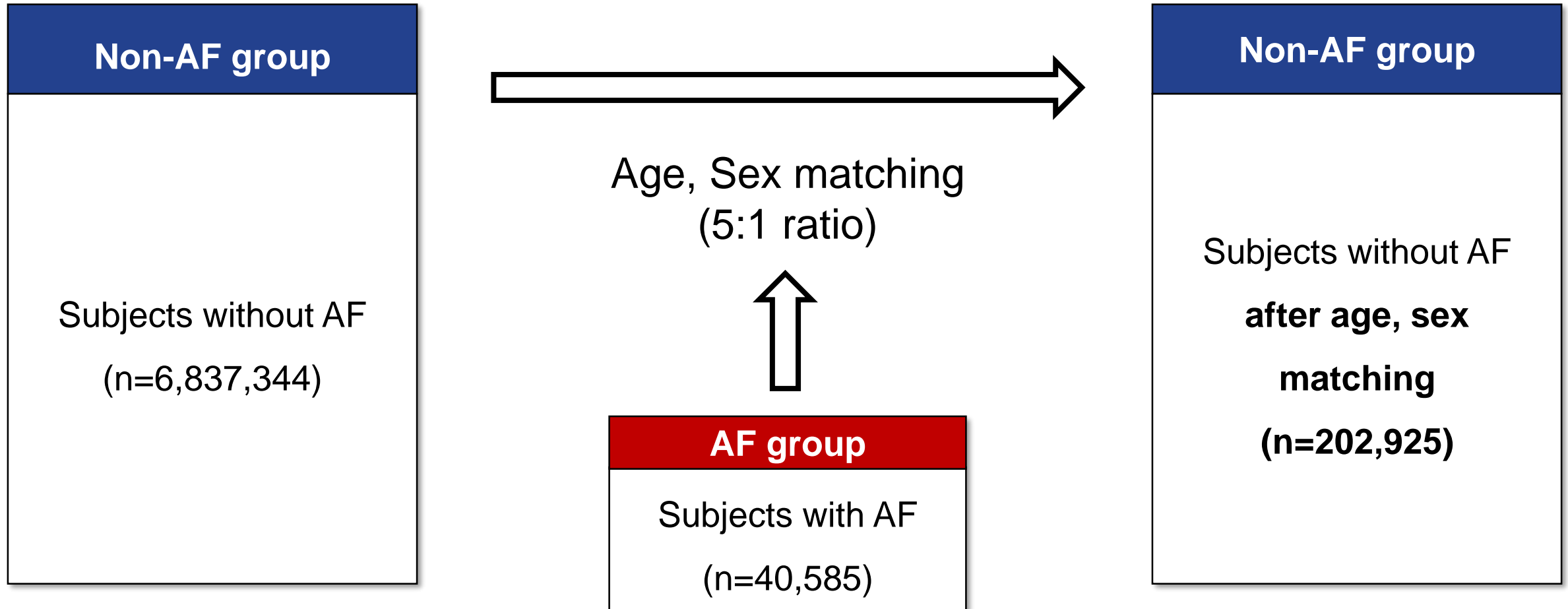
	ICD-10 codes		ICD-10 codes
AB	Certain infectious and parasitic diseases (A00-B99)	J	Diseases of the respiratory system (J00-J99)
CD	Neoplasms (C00-D48)	K	Diseases of the digestive system (K00-K93)
D	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	L	Diseases of the skin and subcutaneous tissue (L00-L99)
E	Endocrine, nutritional and metabolic diseases (E00-E90)	M	Diseases of the musculoskeletal system and connective tissue (M00-M99)
F	Mental and behavioral disorders (F00-F99)	N	Diseases of the genitourinary system (N00-N99)
G	Diseases of the nervous system (G00-G99)	O	Pregnancy, childbirth and the puerperium (O00-O99)
H1	Diseases of the eye and adnexa (H00-H59)	Q	Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)
H2	Diseases of the ear and mastoid process (H60-H95)	R	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)
I	Diseases of the circulatory system (I00-I99)	ST	Injury, poisoning and certain other consequences of external causes (S00-T98)
I₂₀₋₂₅	Ischemic heart diseases (I20-I25)	Z-U	Z00-U99
I₆₀₋₆₉	Cerebrovascular diseases (I60-69)		



Method – Diagnostic codes of ICD-10

ICD-10 codes		ICD-10 codes	
AB	Certain infectious and parasitic diseases (A00-B99)	J	Diseases of the respiratory system (J00-J99)
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I₂₀₋₂₅	Ischemic heart diseases (I20-I25)	Z-U	Z00-U99
I₆₀₋₆₉	Cerebrovascular diseases (I60-69)		

Method – 5:1 matching (age & sex)



Method – Grouping upon CHA₂DS₂-VASc score

AF group
Subjects with AF
(n=40,585)

CVS 0

(n=1,299)

CVS 1

(n=6,779)

CVS 2

(n=9,541)

CVS 3

(n=9,036)

CVS 4

(n=6,625)

CVS 5

(n=4,123)

CVS 6

(n=2,082)

CVS ≥ 7

(n=1,100)

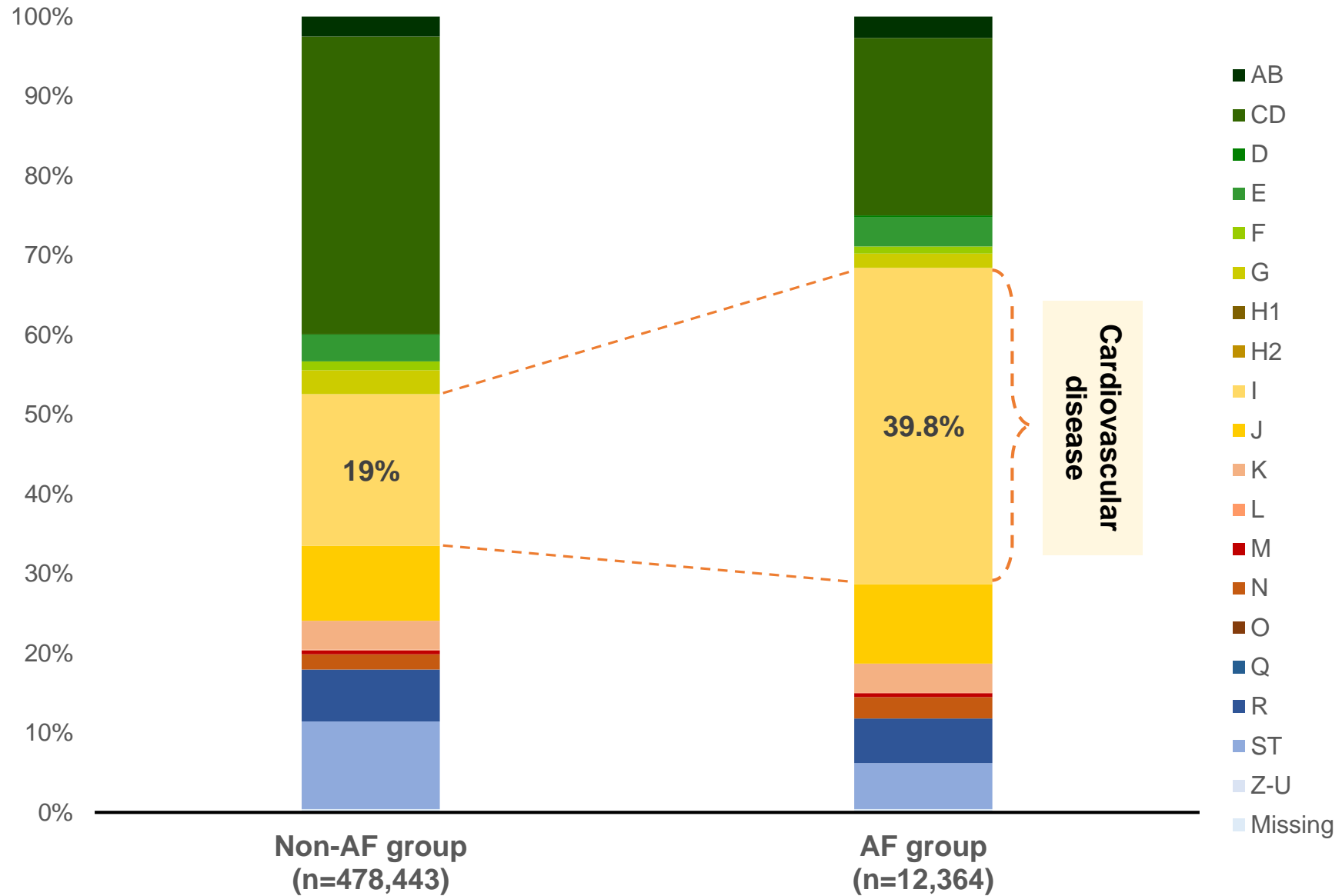


Baseline Characteristics (before matching)

	Non-AF (n=6,837,344)	AF (n=40,585)	p-value
Age, years	54.4 ± 10.5	64.9 ± 10.1	<0.001
≥ 65 years	1,300,254 (19.0)	22,405 (55.2)	<0.001
Sex, men	3,433,968 (50.2)	25,000 (61.6)	<0.001
Comorbidity			
Hypertension	2,313,442 (33.8)	29,731 (73.3)	<0.001
Diabetes mellitus	806,526 (11.8)	9,429 (23.2)	<0.001
Dyslipidemia	1,561,650 (22.8)	15,055 (37.1)	<0.001
Ischemic heart disease	386,537 (5.7)	15,680 (38.6)	<0.001
Ischemic stroke	152,462 (2.2)	5,950 (14.7)	<0.001
Chronic kidney disease	562,798 (8.2)	9,033 (22.5)	<0.001
Cancer	144,068 (2.1)	1,692 (4.2)	<0.001
Physical examination			
Body mass index (kg/m ²)	24.0 ± 3.4	24.3 ± 3.2	<0.001
<18.5	157,175 (2.3)	1,176 (2.9)	
18.5 to <23	2,474,524 (36.2)	12,464(30.7)	
23 to 25	1,821,273(26.6)	10,558 (26.0)	
25 to 30	2,158,079 (31.6)	14,628(36.0)	
≥30	226,293 (3.3)	1,759 (4.3)	
Waist circumference (cm)	81.2 ± 8.9	84.4 ± 8.8	<0.001
Central obesity, yes	1,544,028 (22.6)	13,706 (33.8)	<0.001



Proportion of Each Cause of Death



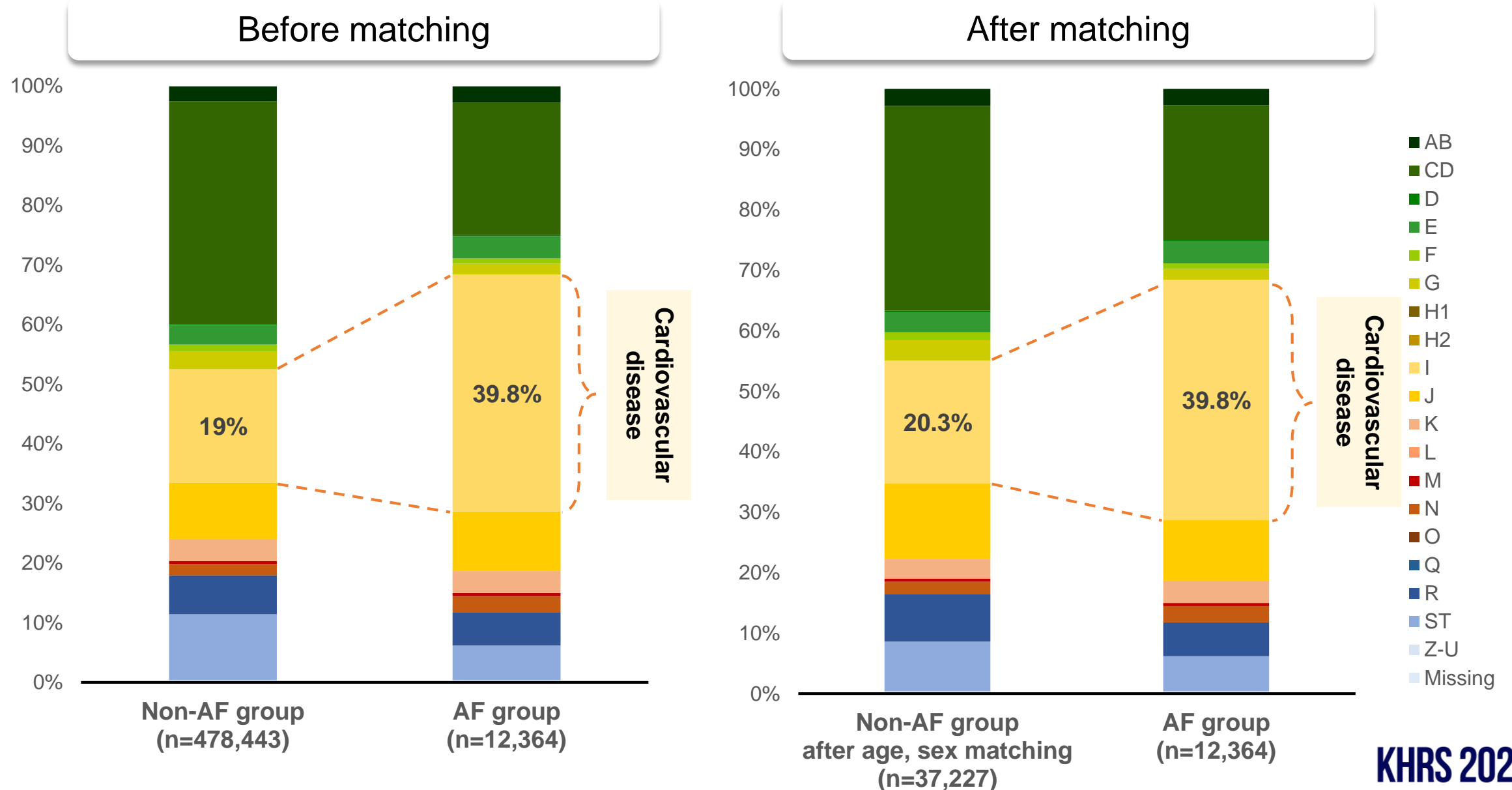
Incidence rate and Hazard ratio of Each Cause of Death

	IR		Adjusted HR (95% CI) †	P-value
	Non-AF	AF		
All-cause	6.94	34.24	1.739 (1.708-1.771)	<0.001
Infectious diseases	0.18	0.91	1.717 (1.537,1.920)	<0.001
Neoplastic diseases	2.59	7.64	1.258 (1.211,1.307)	<0.001
Hematologic diseases	0.22	1.26	1.479 (1.346,1.626)	<0.001
Endocrine, nutritional, metabolic diseases	0.08	0.30	1.284 (1.058,1.558)	0.011
Neurological diseases	0.21	0.63	1.009 (0.884,1.151)	0.895
Cardiovascular diseases	1.32	13.62	2.899 (2.814,2.985)	<0.001
Ischemic heart diseases	0.35	2.48	1.768 (1.652,1.893)	<0.001
Cerebrovascular diseases	0.52	5.16	2.911 (2.775,3.054)	<0.001
Respiratory diseases	0.65	3.43	1.560 (1.473,1.652)	<0.001
Gastrointestinal diseases	0.25	1.24	2.052 (1.864,2.258)	<0.001
Skin, subcutaneous tissue diseases	0.01	0.03	1.112 (0.625,1.978)	0.717
Musculoskeletal, connective tissue diseases	0.03	0.16	1.558 (1.194,2.034)	0.001
Genitourinary diseases	0.13	0.91	1.620 (1.448,1.812)	<0.001

† Age, sex, level of smoking, level of alcohol consumption, regular physical activities, diabetes mellitus, dyslipidemia, CKD, cancer history, depression, ischemic heart disease, stroke adjusted



Proportion of Each Cause of Death (age, sex 5:1 matching)



Incidence rate & Hazard ratio of Each Cause of Death (age, sex 5:1 matching)

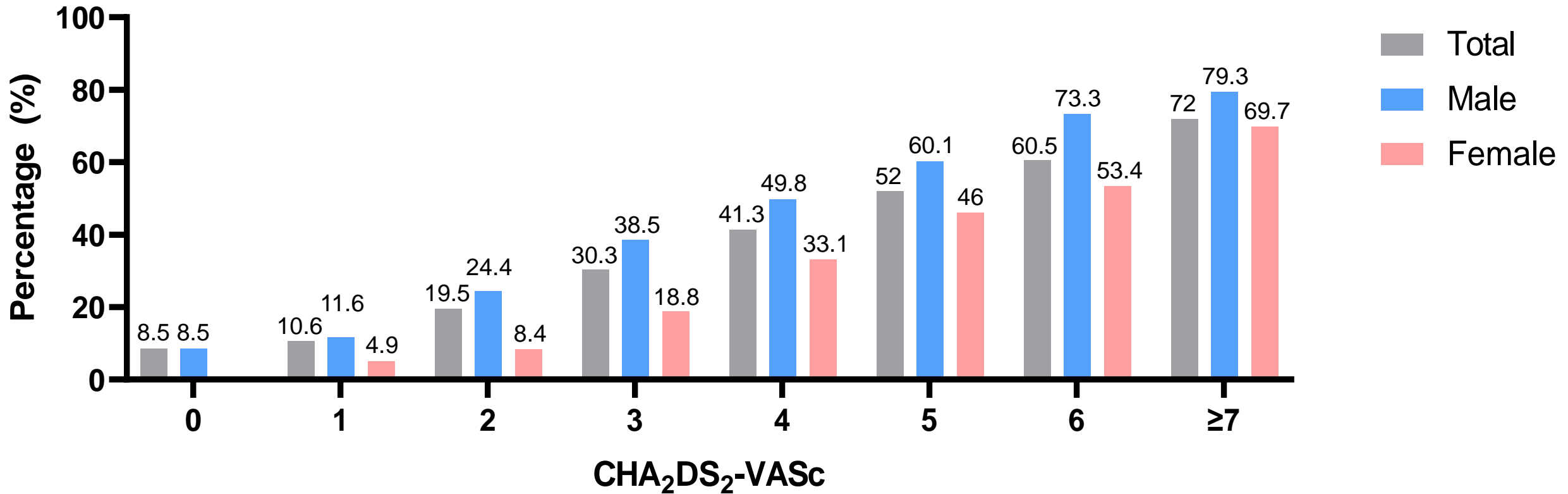
	IR		Adjusted HR (95% CI) †	P-value
	Non-AF	AF		
All-cause	19.05	34.24	1.778 (1.740,1.818)	<0.001
Infectious diseases	0.54	0.91	1.694 (1.483,1.935)	<0.001
Neoplastic diseases	6.43	7.64	1.280 (1.225,1.338)	<0.001
Hematologic diseases	0.63	1.26	1.514 (1.350,1.697)	<0.001
Endocrine, nutritional, metabolic diseases	0.25	0.30	1.270 (1.018,1.585)	0.034
Neurological diseases	0.65	0.63	1.016 (0.875,1.179)	0.837
Cardiovascular diseases	3.87	13.62	3.082 (2.963,3.205)	<0.001
Ischemic heart diseases	0.99	2.48	1.880 (1.724,2.049)	<0.001
Cerebrovascular diseases	1.52	5.16	2.981 (2.799,3.175)	<0.001
Respiratory diseases	2.38	3.43	1.554 (1.453,1.662)	<0.001
Gastrointestinal diseases	0.58	1.24	2.247 (1.995,2.530)	<0.001
Skin, subcutaneous tissue diseases	0.03	0.03	1.198 (0.629,2.284)	0.582
Musculoskeletal, connective tissue diseases	0.09	0.16	1.716 (1.243,2.367)	0.001
Genitourinary diseases	0.40	0.91	1.714 (1.492,1.969)	<0.001

† Age, sex, level of smoking, level of alcohol consumption, regular physical activities, diabetes mellitus, dyslipidemia, CKD, cancer history, depression, ischemic heart disease, stroke adjusted



All Cause Death according to CHA₂DS₂-VASc Score

Percentage of All Cause Death



* **CHA₂DS₂-VASc score** : 65 and 74 years : 1 pt. / female sex : 1 pt. / hypertension : 1 pt. / diabetes mellitus : 1 pt. / heart failure : 1 pt. / vascular disease (prior myocardial infarction or peripheral artery disease) : 1pt. / history of stroke/TIA/thromboembolism : 2 pts. / age ≥75 years : 2 pts.

Incidence rate & Hazard ratio according to CHA₂DS₂-VASc Score - All Cause Death

CVS	Total				Male				Female			
	IR	Adjusted HR ¶ (95% CI)	P-value		IR	Adjusted HR ¶ (95% CI)	P-value		IR	Adjusted HR ¶ (95% CI)	P-value	
0	8.60	1	<0.001		8.60	1	<0.001				<0.001	
1	10.75	1.060 (0.868,1.295)			11.82	1.083 (0.885,1.324)			4.84	1		
2	20.63	1.346 (1.109,1.633)			26.47	1.432 (1.178,1.741)			8.34	1.157 (0.853,1.570)		
3	33.60	1.643 (1.353,1.994)			45.04	1.778 (1.460,2.166)			19.34	1.463 (1.092,1.959)		
4	49.10	2.017 (1.658,2.454)			63.30	2.150 (1.761,2.626)			36.93	1.867 (1.391,2.505)		
5	66.87	2.462 (2.019,3.003)			84.36	2.510 (2.045,3.080)			55.89	2.379 (1.768,3.200)		
6	84.93	2.927 (2.390,3.585)			118.64	3.021 (2.438,3.742)			69.69	2.781 (2.059,3.756)		
≥7	117.99	3.833 (3.110,4.723)			150.17	3.538 (2.782,4.500)			109.68	3.723 (2.744,5.053)		

¶ Age, sex, level of smoking, level of alcohol consumption, regular physical activities



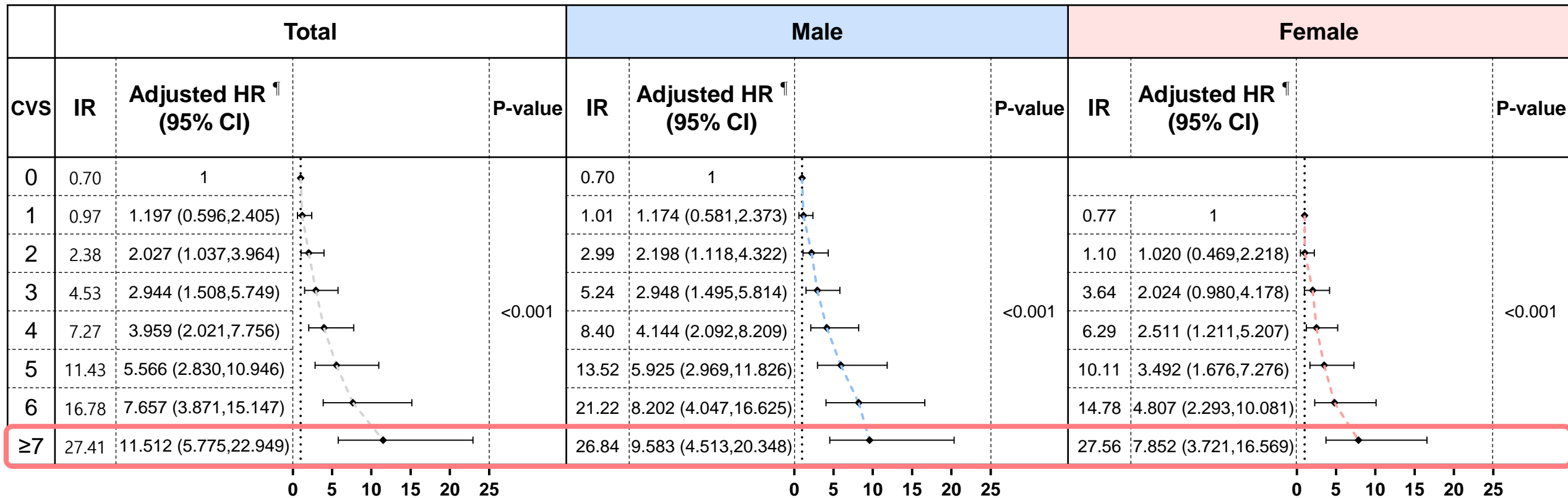
Incidence rate & Hazard ratio according to CHA₂DS₂-VASc Score - Cardiovascular Death

	Total				Male				Female			
CVS	IR	Adjusted HR ¶ (95% CI)		P-value	IR	Adjusted HR ¶ (95% CI)		P-value	IR	Adjusted HR ¶ (95% CI)		P-value
0	2.401	1		<0.001	2.40	1		<0.001				<0.001
1	3.090	1.107 (0.758,1.615)			3.34	1.155 (0.790,1.690)			1.74	1		
2	6.816	1.675 (1.165,2.409)			8.16	1.835 (1.271,2.650)			3.98	1.589 (0.966,2.614)		
3	12.74	2.352 (1.636,3.381)			15.31	2.654 (1.835,3.837)			9.53	2.167 (1.341,3.504)		
4	20.52	3.137 (2.177,4.519)			23.02	3.499 (2.411,5.077)			18.38	2.880 (1.778,4.665)		
5	28.63	3.894 (2.694,5.629)			31.57	4.283 (2.931,6.258)			26.78	3.575 (2.199,5.810)		
6	38.76	4.901 (3.374,7.119)			46.76	5.540 (3.743,8.199)			35.14	4.416 (2.704,7.211)		
≥7	58.10	6.763 (4.625,9.891)			64.57	7.206 (4.712,11.018)			56.43	6.109 (3.720,10.03)		

¶ Age, sex, level of smoking, level of alcohol consumption, regular physical activities



Incidence rate & Hazard ratio according to CHA₂DS₂-VASc Score - Cerebrovascular Death



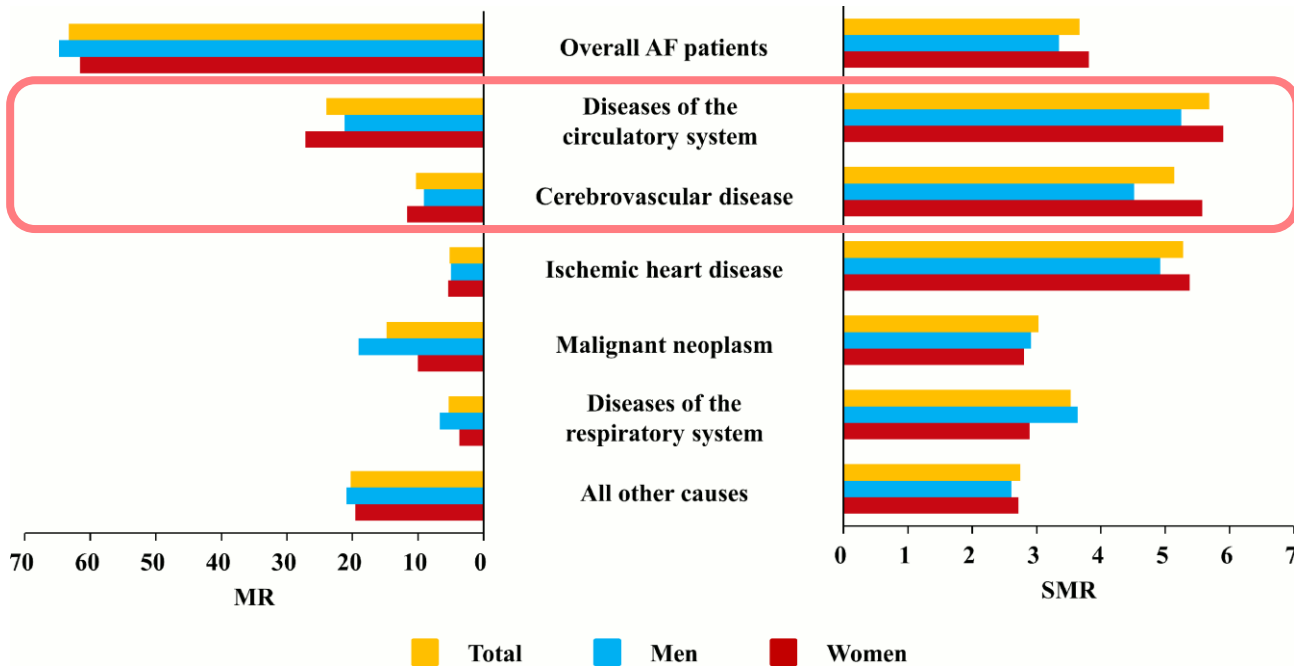
Risk of each cause of death **well-stratified** according to CHA₂DS₂-VAsC Score



¶ Age, sex, level of smoking, level of alcohol consumption, regular physical activities

Discussion

1,025,340 individuals (2.2%) of Korean population in 2002 followed up through 2002 - 2013



S3 Table. Major specific causes of death in patients with atrial fibrillation according to sex (ICD-10 code).

Rank	Total		Men		Women	
	Cause of death	N (%)	Cause of death	N (%)	Cause of death	N (%)
1	Cerebral infarction (I63)	345 (7.8)	Malignant neoplasm of bronchus and lung (C34)	216 (8.9)	Cerebral infarction (I63)	194 (9.5)
2	Malignant neoplasm of bronchus and lung (C34)	266 (6.0)	Cerebral infarction (I63)	152 (6.3)	Senility (R54)	135 (6.6)
3	Acute myocardial infarction (I21)	221 (5.0)	Acute myocardial infarction (I21)	117 (4.8)	Sequelae of cerebrovascular disease (I69)	109 (5.3)
4	Senility (R54)	200 (4.5)	Malignant neoplasm of liver and intrahepatic bile ducts (C22)	99 (4.1)	Acute myocardial infarction (I21)	104 (5.1)
5	Sequelae of cerebrovascular disease (I69)	198 (4.5)	Chronic obstructive pulmonary disease (J44)	90 (3.7)	Heart failure (I50)	86 (4.2)
6	Type 2 diabetes mellitus (E11)	157 (3.6)	Gastric cancer (C16)	89 (3.7)	Type 2 diabetes mellitus (E11)	84 (4.1)



Discussion

- Despite the increase in prescriptions of oral anticoagulants, AF patients still have high risk of death due to cerebrovascular diseases
- Anticoagulation strategies for patients with high CHA₂DS₂-VASc score might be individualized



Limitation

- Considering characteristics of observational study, **causality cannot be proven (only relationship)**
- **Specific disease entities** beyond ICD-10 codes are not shown
- Exact anticoagulation strategies for each patient not included



Summary

- A total of 490,807 deaths were reported during follow-up period
- In the AF group, **cardiovascular diseases were the most common cause of death** (39.8% of all-death)
- The AF group had about **3 times higher risk** of death due to cardiovascular diseases and cerebrovascular diseases
- Risk of all cause death, cardiovascular death, cerebrovascular death are **well stratified upon CHA₂DS₂-VASc score**



Conclusion

Patients with atrial fibrillation are more prone to cardiovascular and cerebrovascular deaths.

Integrated care to control risk factors related with cardiovascular diseases should be emphasized.

Treatment strategy for cerebrovascular diseases should be optimized.

