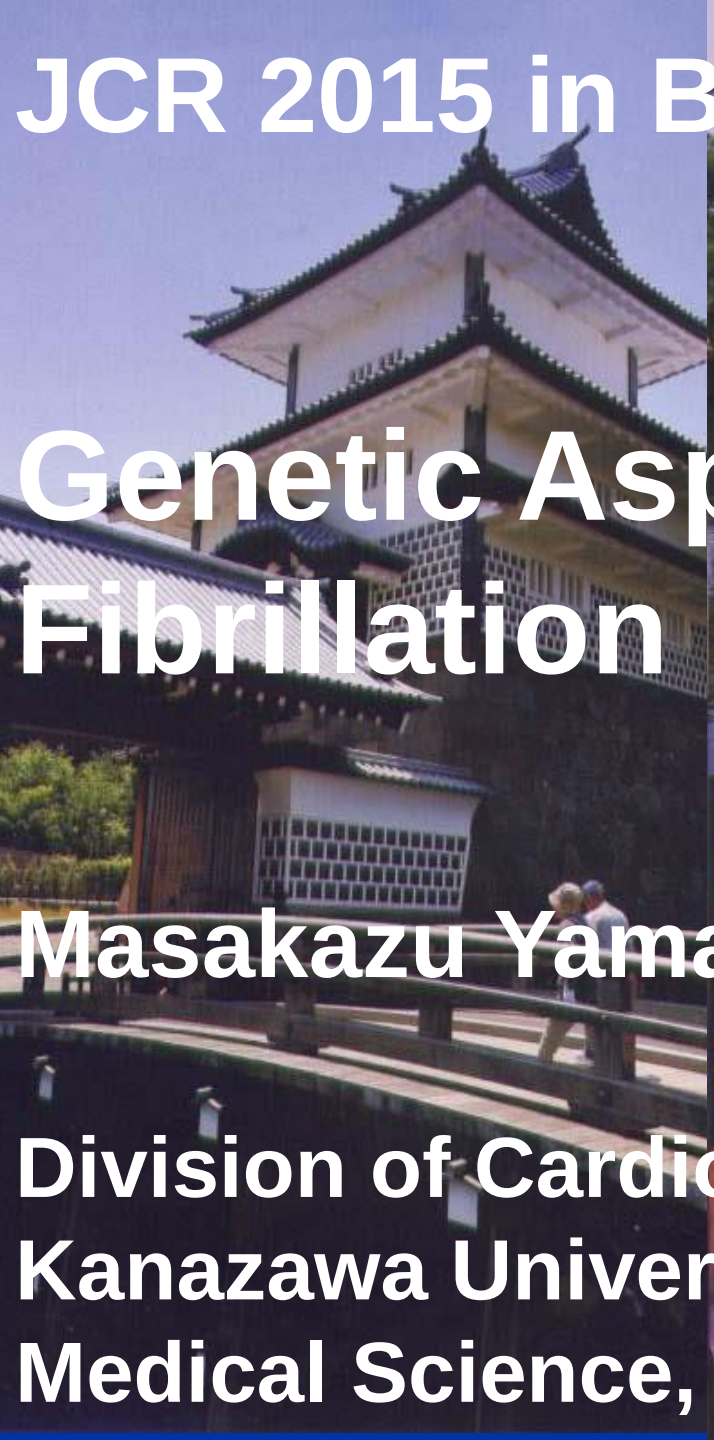
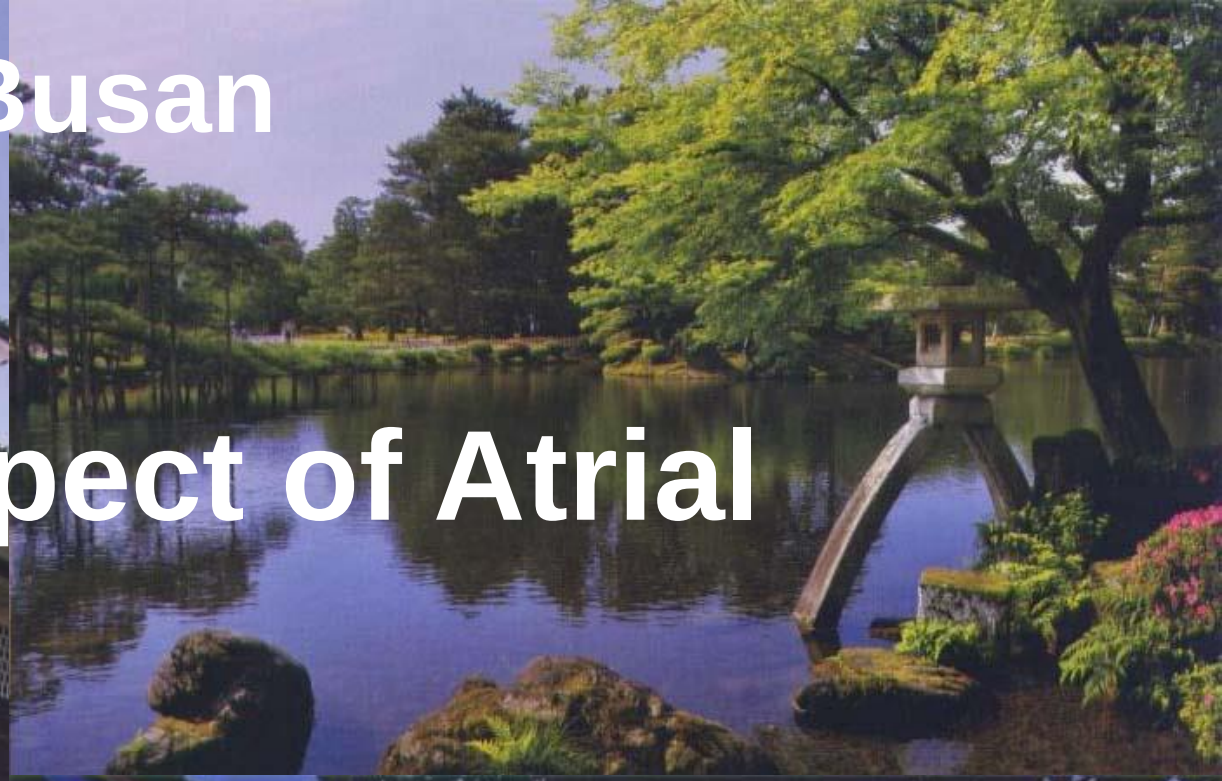
JCR 2015 in Busan

Genetic Aspect of Atrial Fibrillation





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JCR 2015 in Busan

Genetic Aspect of Atrial Fibrillation

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COI

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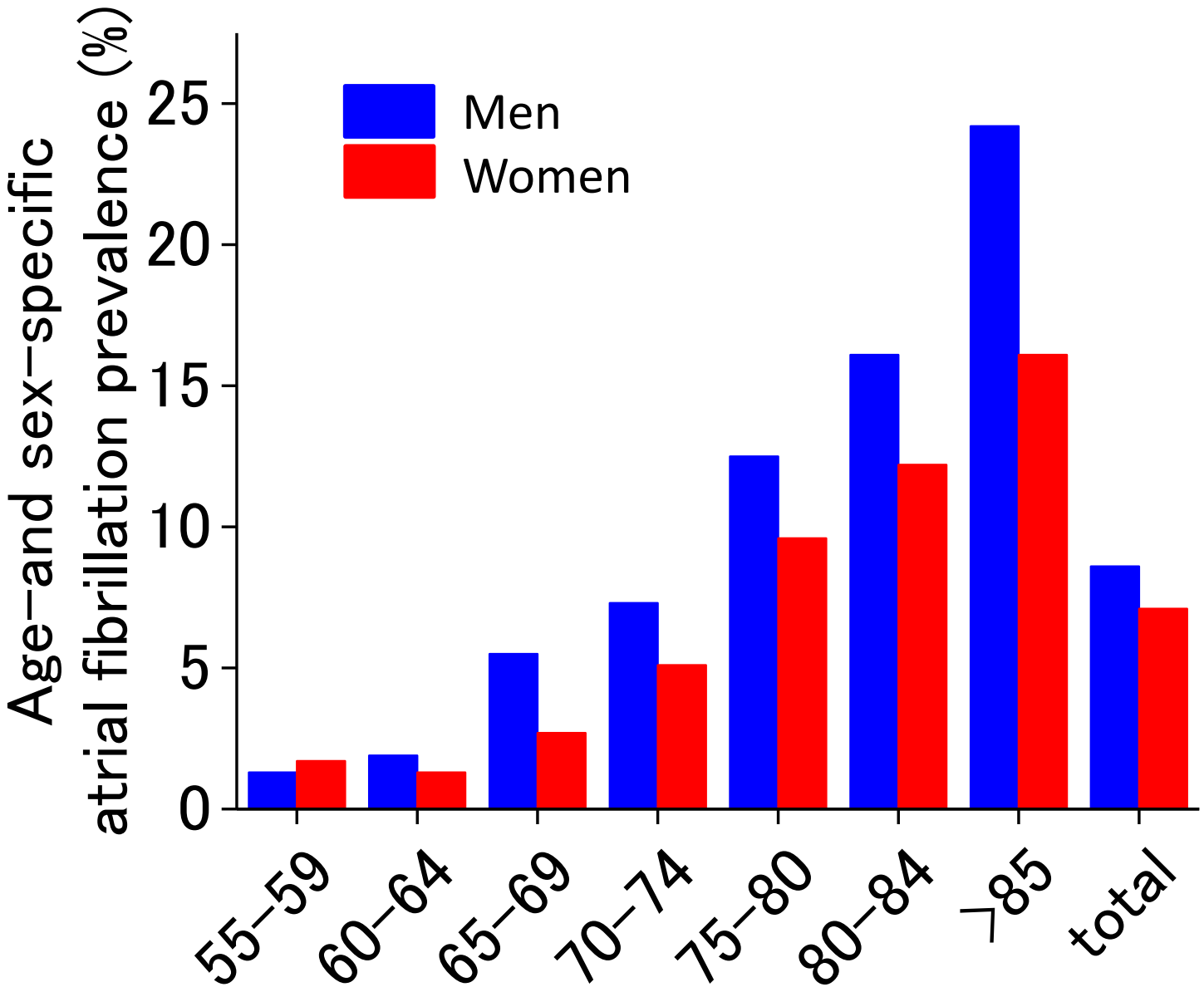
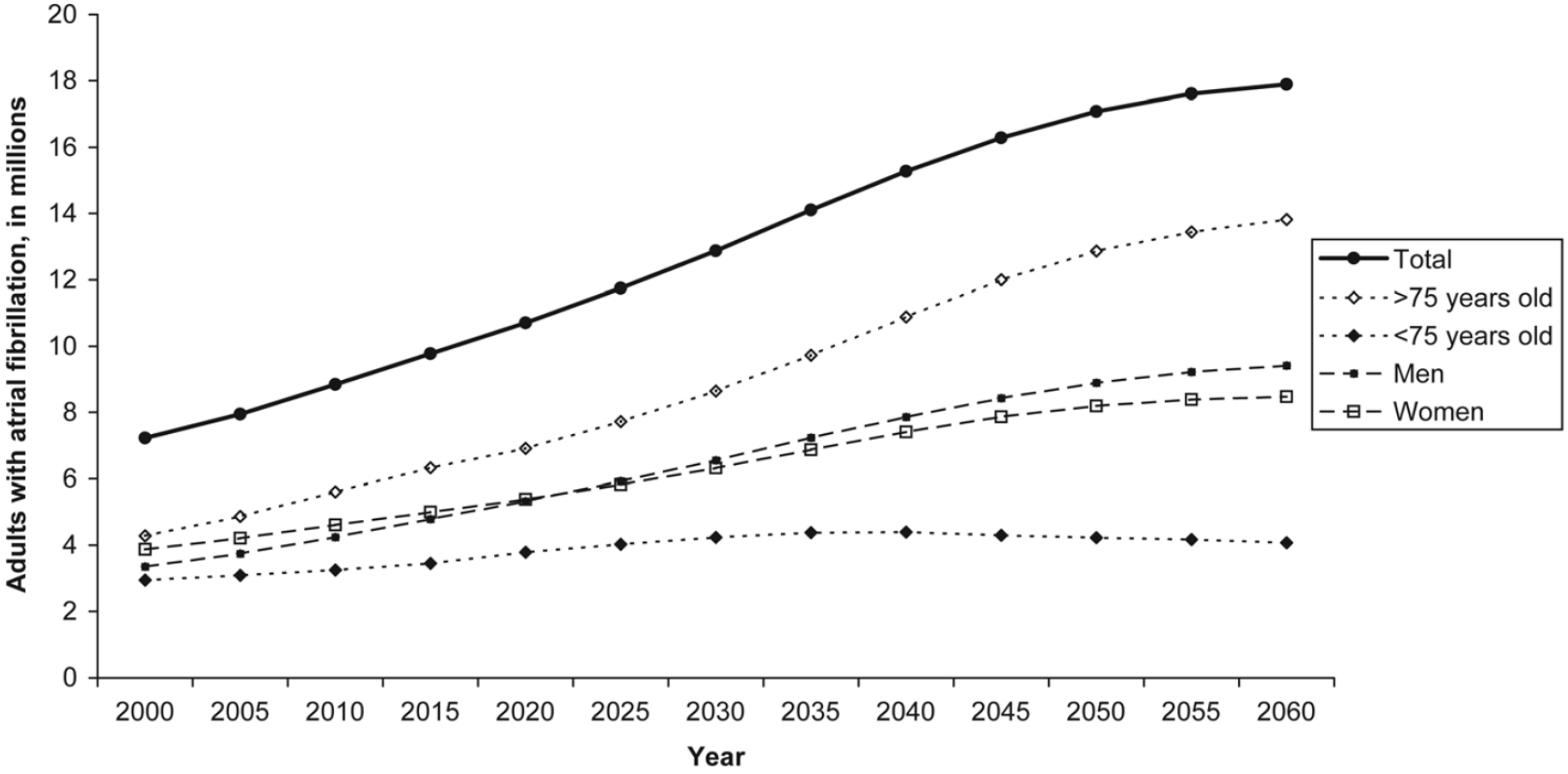
Age- and sex-specific atrial fibrillation prevalence



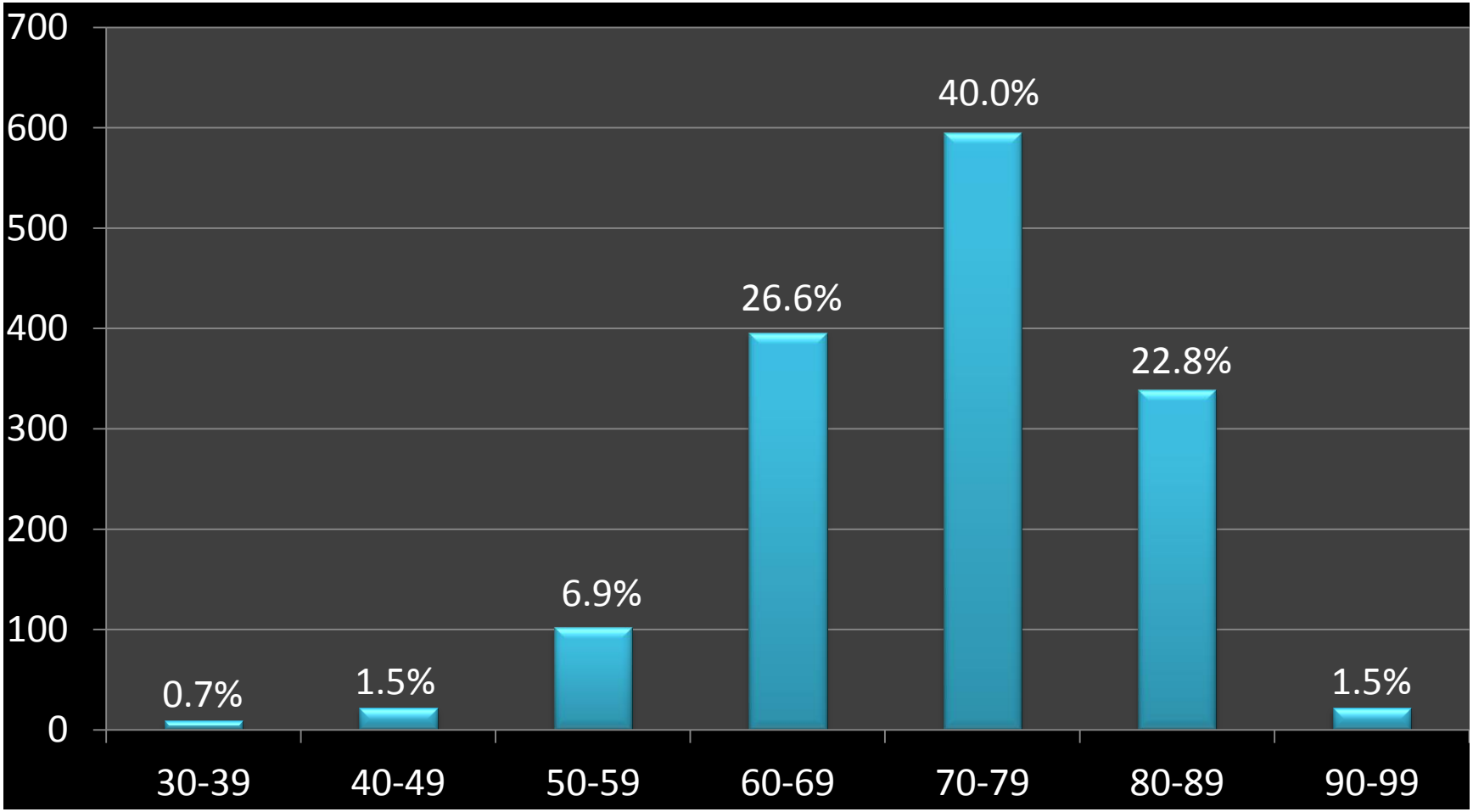
(Krijthe, et al, European Heart Journal 2013)

Projected number of adults with atrial fibrillation in the European Union between 2000 and 2060

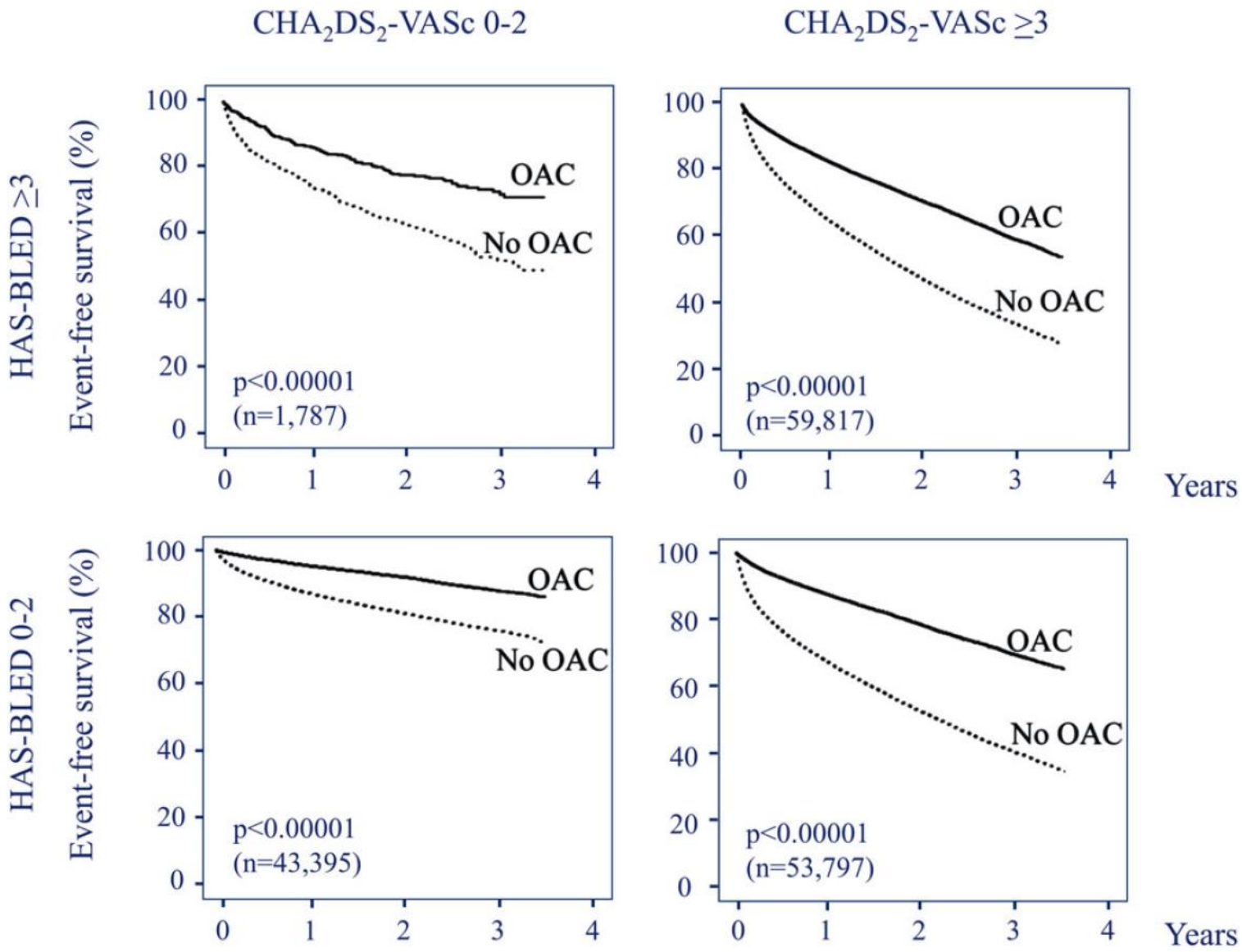


(Krijthe, et al, European Heart Journal 2013)

Age groups of atrial fibrillation

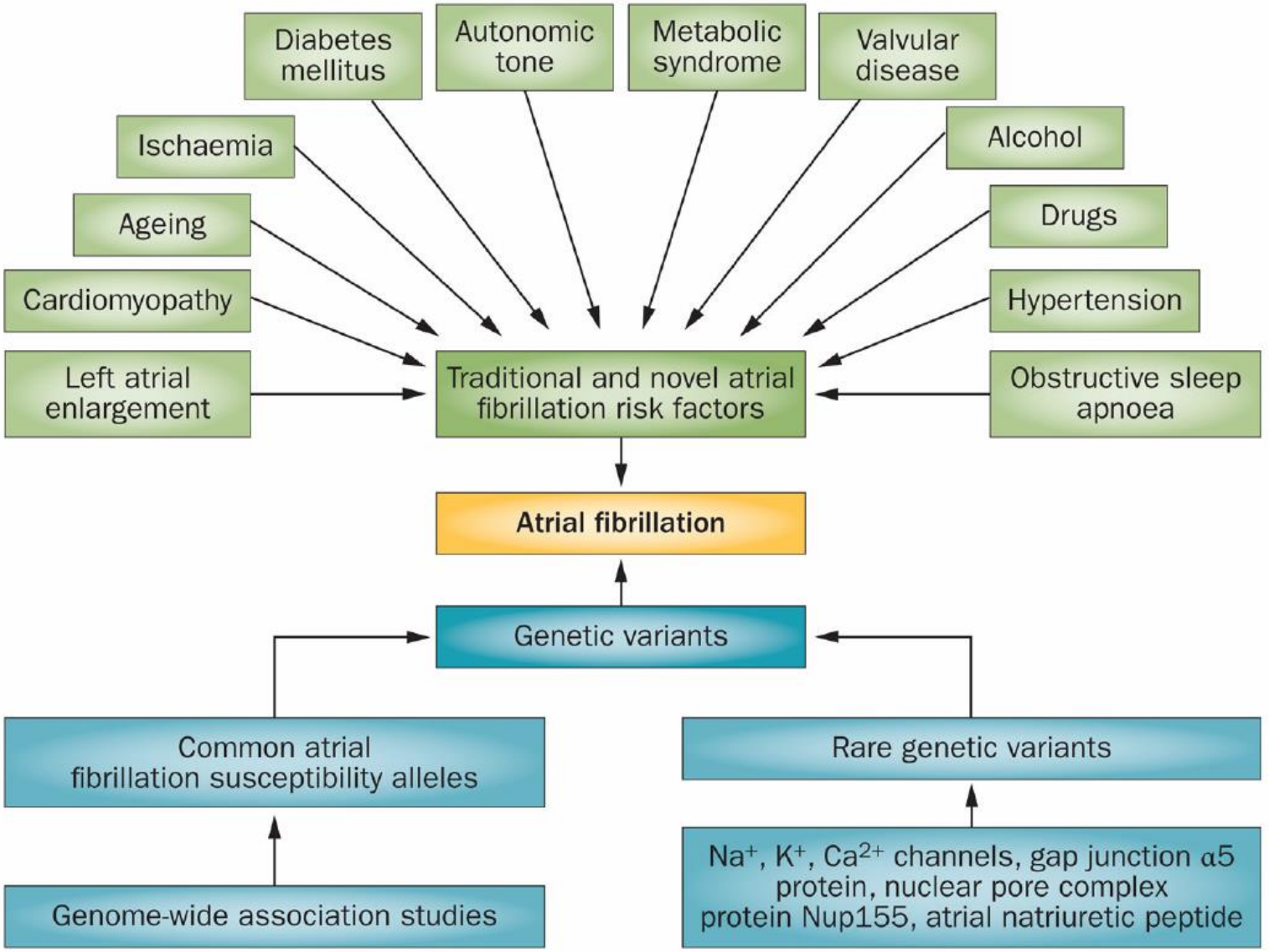


Relative benefit of oral anticoagulants vs. no oral anticoagulant



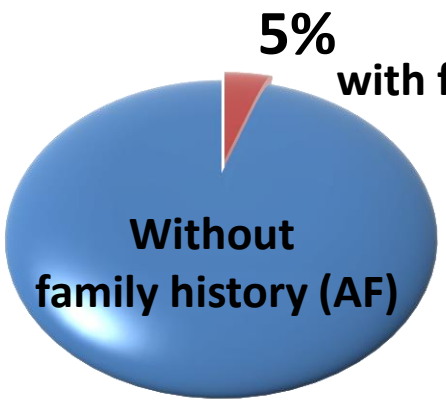
(Andreotti et al., European Heart Journal, 2015)

The two-hit hypothesis; a combination of genetic and an acquired risk factor is required for development of atrial fibrillation

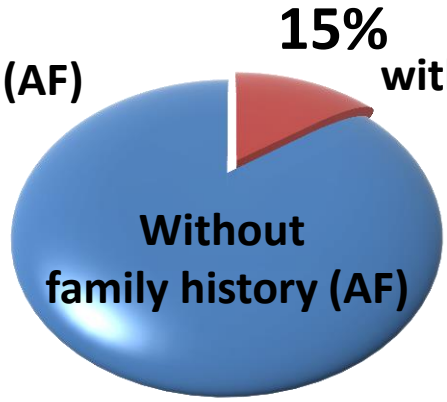


(Darbar, et al, Nat Rev Cardiol. 2013)

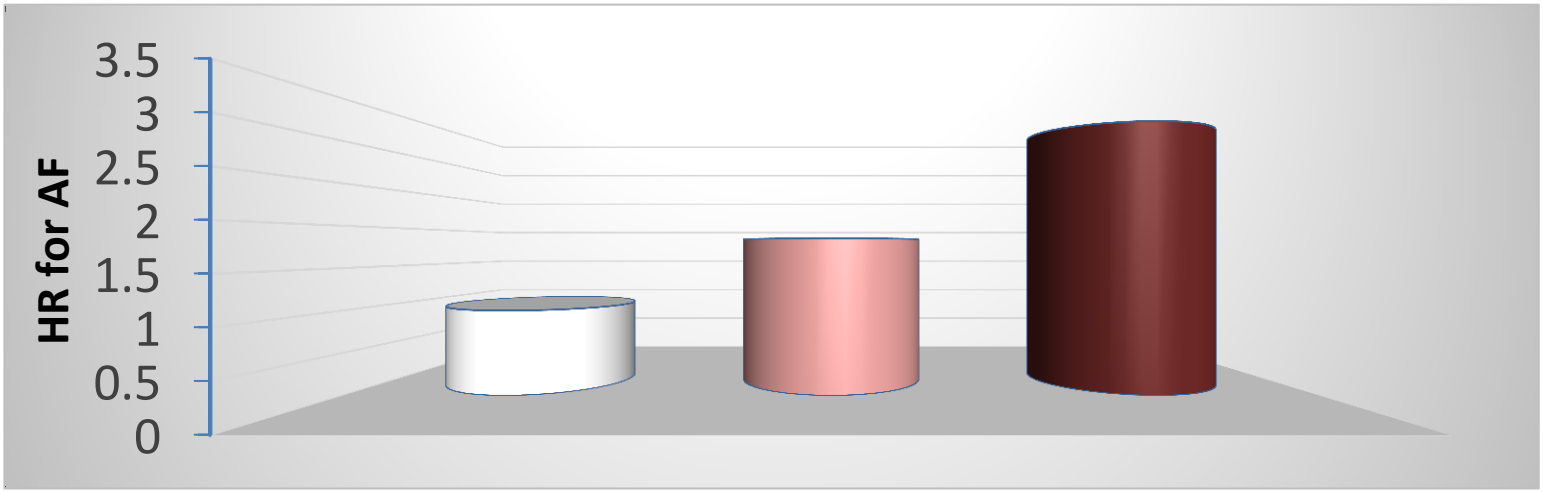
Atrial Fibrillation is heritable



ALL AF



lone AF



JAMA. 2004;291:2851-2855

Genetic architecture

- Dyslipidemia
- Diabetes
- AF

Family-based studies

Population-based studies

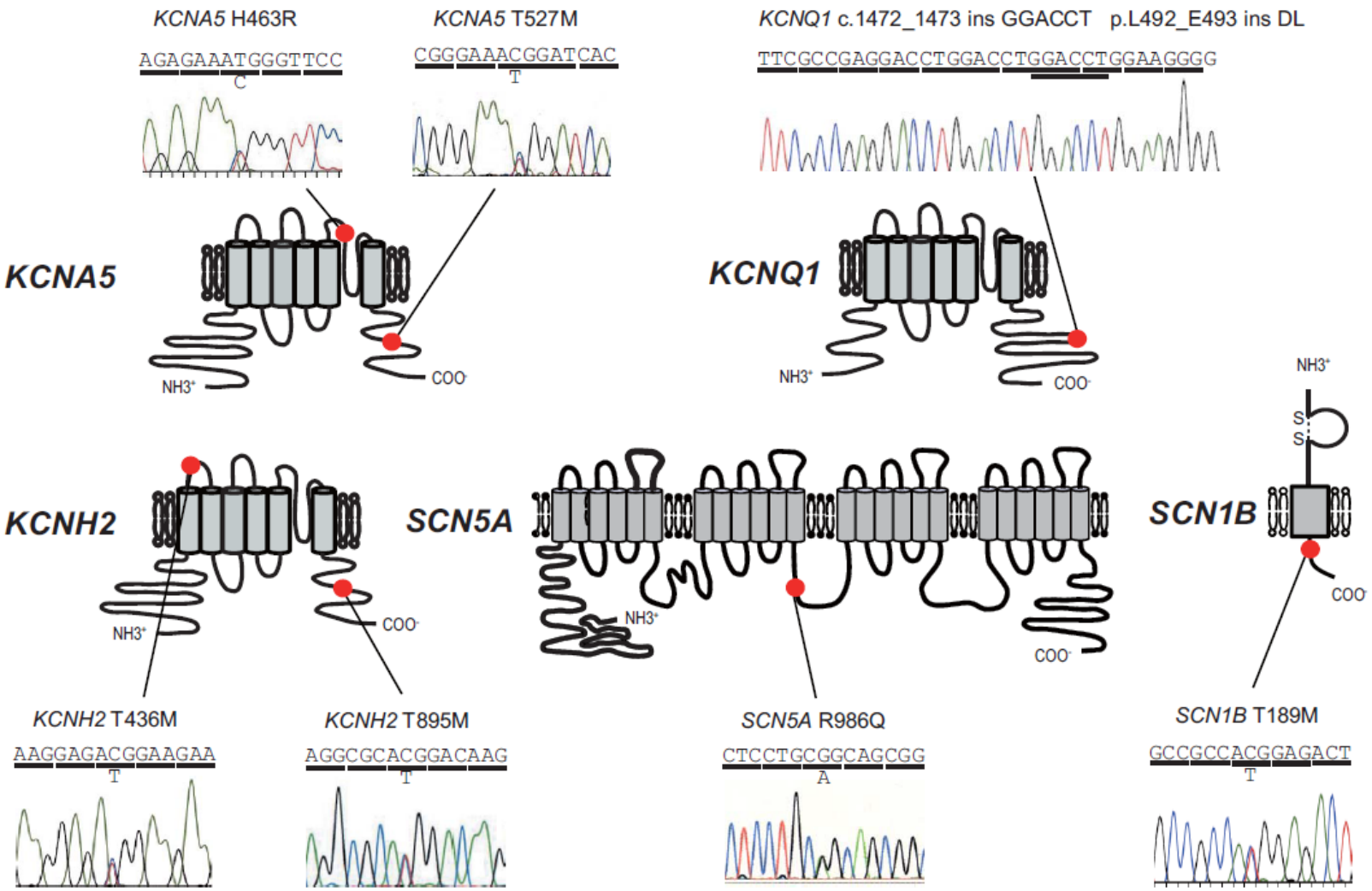
- FH
- HCM
- Long QT

Effect Size (Odds ratio)

Allele Frequency

Kathiresan S. ***Cell*** 2012;148(6):1242-57.

Seven rare variants in cardiac ion channels were identified in the study cohort of 90 individuals with lone AF



（Hayashi et al., Circ Arrhythmia Electrophysiol. 2015 ）

In vitro cellular electrophysiology and *In silico* prediction analysis

Genotype	MAF in ExAC (%)	Electrophysiological abnormality	Score CADD
KCNA5 H463R	N/A	Loss of function	14.25 Deleterious
KCNA5 T527M	0.0236	Gain of function	19.35 Deleterious
KCNQ1 L492_E493 ins DL	N/A	No change	N/A
KCNH2 T436M	0.00163	Gain of function	1.52
KCNH2 T895M	N/A	Gain of function	17.78 Deleterious
SCN5A R986Q	0.00195	Loss of function	11.17 Deleterious
SCN1B T189M	N/A	Gain of function	15.27 Deleterious

MAF, Minor allele frequency; ExAC, Exome Aggregation Consortium; CADD, Combined Annotation Dependent Depletion

（Hayashi et al., Circ Arrhythmia Electrophysiol. 2015 ）

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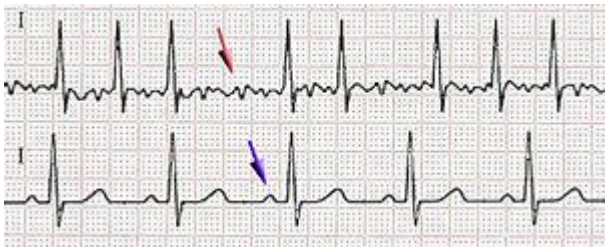
Phenotype-Genotype association



Phenotype

Genotype

Phenotype Modeling

Quality Control

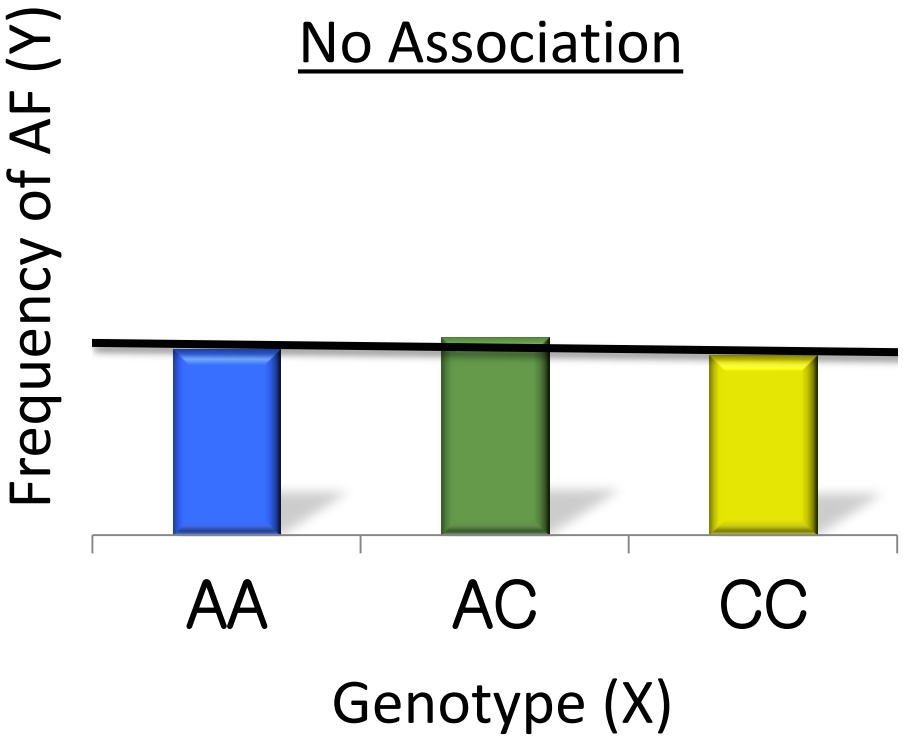
Analysis

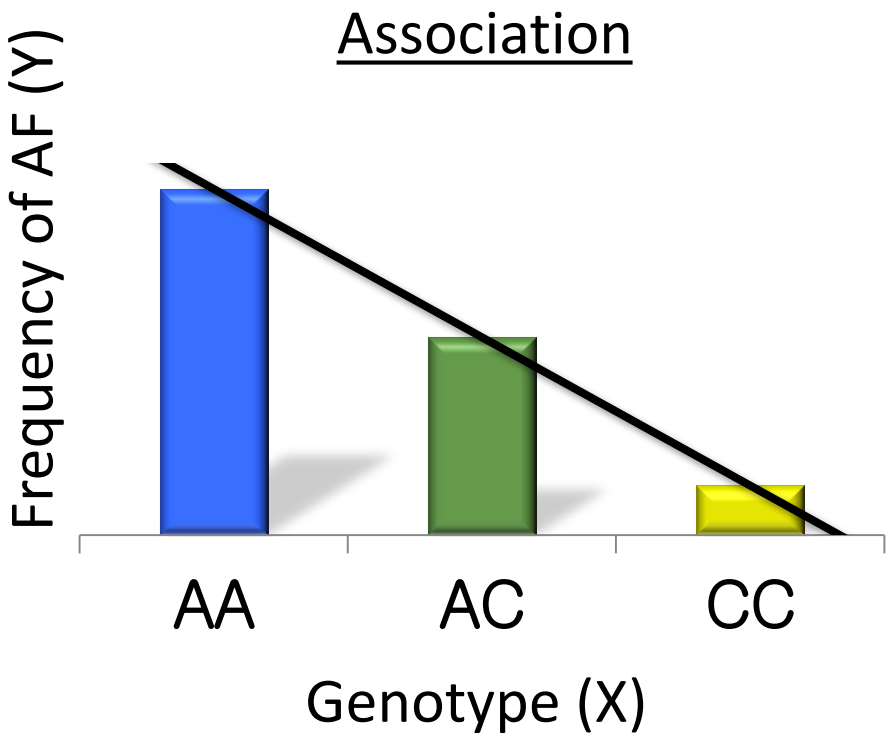
Courtesy: Illumina

Association testing (single-marker testing)

Threshold of significance (p value < 5×10^{-8}) :

for 1M variants on the array





Genome-wide association studies-derived risk loci for AF

Locus	SNP	RR	P value	Closest gene	Relative location
4q25	rs6817105	1.64	1.8×10^{-74}	*PITX2*	150-kb upstream
16q22	rs2106261	1.24	3.2×10^{-16}	*ZFHX3*	Intronic
1q21	rs6666258	1.18	2.0×10^{-14}	*KCNN3*	Intronic
1q24	rs3903239	1.14	9.1×10^{-11}	*PRRX1*	46-kb upstream
7q31	rs3807989	0.90	9.6×10^{-11}	*CAV1*	Intronic
14q23	rs1152591	1.13	6.2×10^{-10}	*SYNE2*	Intronic
9q22	rs10821415	1.11	7.9×10^{-9}	*C9orf3*	Intronic
15q24	rs7164883	1.19	1.3×10^{-8}	*HCN4*	Intronic
10q22	rs10824026	0.87	1.7×10^{-8}	*MYOZ1*	20-kb upstream

(Nathan, et al, Circ Res. 2014)

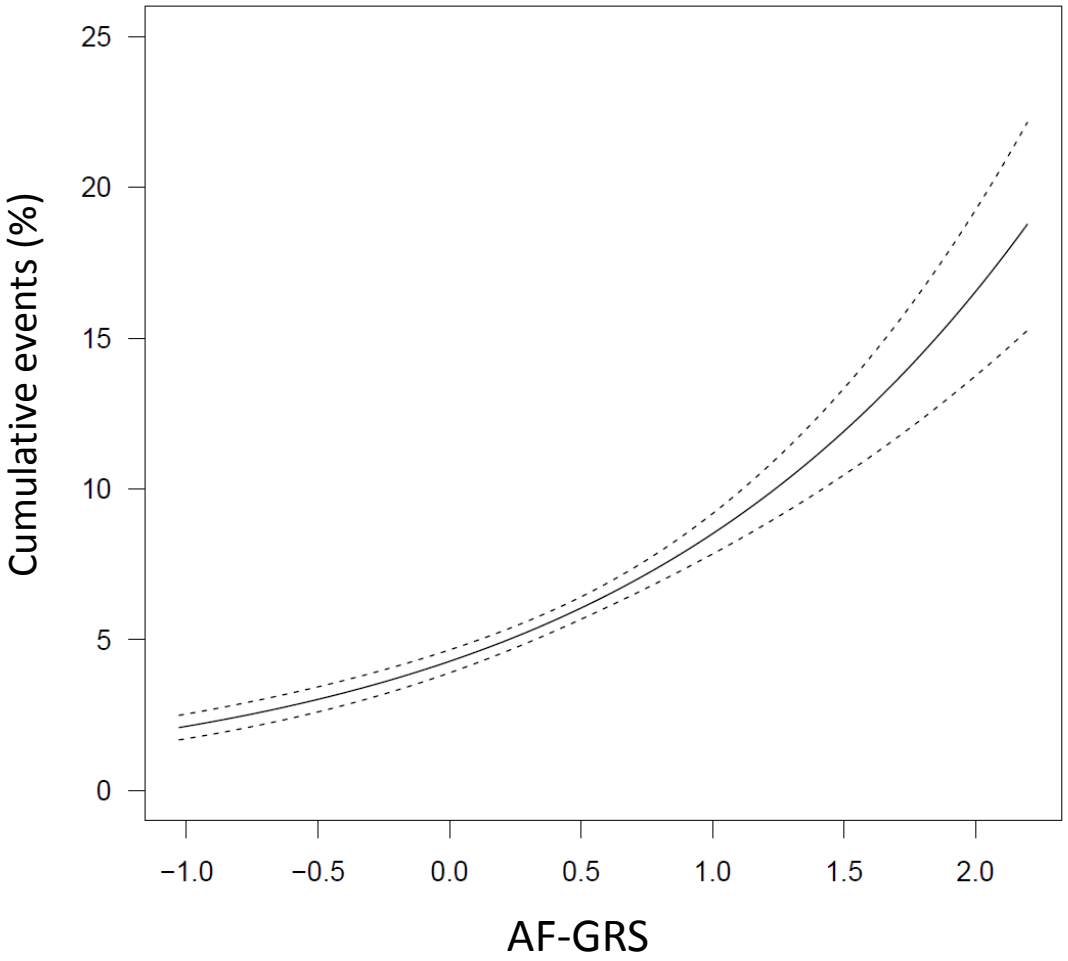
Association of SNP with incident AF in the MDC study

Locus	Gene	SNP	Modeled allele	Other allele	MAF‡	Risk estimate from literature (weight)	Risk estimate from MDC study	
							HR (95%CI)	P value
1q21	KCNN3	rs13376333	T	C	0.34	1.13 (0.12)	1.10 (1.03-1.17)	5.5×10^{-3}
1q24	PRRX1	rs3903239	G	A	0.47	1.14 (0.13)	1.11 (1.05-1.19)	6.4×10^{-4}
4q25	PITX2	rs10033464*	T	G	0.09	1.39 (0.33)	1.16 (1.04-1.29)	5.7×10^{-3}
4q25	PITX2	rs2200733†	T	C	0.10	1.72 (0.54)	1.45 (1.32-1.59)	8.1×10^{-15}
4q25	PITX2	rs17570669*	T	A	0.08	0.73 (-0.31)	0.76 (0.67-0.86)	2.4×10^{-5}
4q25	PITX2	rs3853445*	C	T	0.27	0.86 (-0.15)	0.84 (0.78-0.90)	1.8×10^{-6}
7q31	CAV1	rs3807989	A	G	0.41	0.9 (-0.11)	0.90 (0.85-0.96)	2.3×10^{-3}
9q22	C9orf3	rs10821415	A	C	0.41	1.11 (0.10)	1.03 (0.96-1.09)	0.4
10q22	SYNPO2L	rs10824026	G	A	0.16	0.87 (-0.14)	0.83 (0.76-0.91)	6.4×10^{-5}
14q23	SYNE2	rs1152591	A	G	0.49	1.13 (0.12)	1.03 (0.97-1.10)	0.35
15q24	HCN4	rs7164883	G	A	0.17	1.19 (0.17)	1.09 (1.01-1.18)	0.032
16q22	ZFHX3	rs2106261	T	C	0.18	1.24 (0.22)	1.10 (1.01-1.19)	0.025

Model : adjusted for age, sex, BMI, systolic and diastolic blood pressure, use of antihypertensive medications, current smoking, prevalent diabetes, prevalent coronary heart disease, and prevalent heart failure.
*Adjusted for rs2200733 †Adjusted for rs1003346

Tada H, Ellinor PT, Kathiresan S, et al. ***Stroke.*** 2014;45:2856-62.

The probability of a first AF event increased smoothly with increased AF-genetic risk score (GRS)

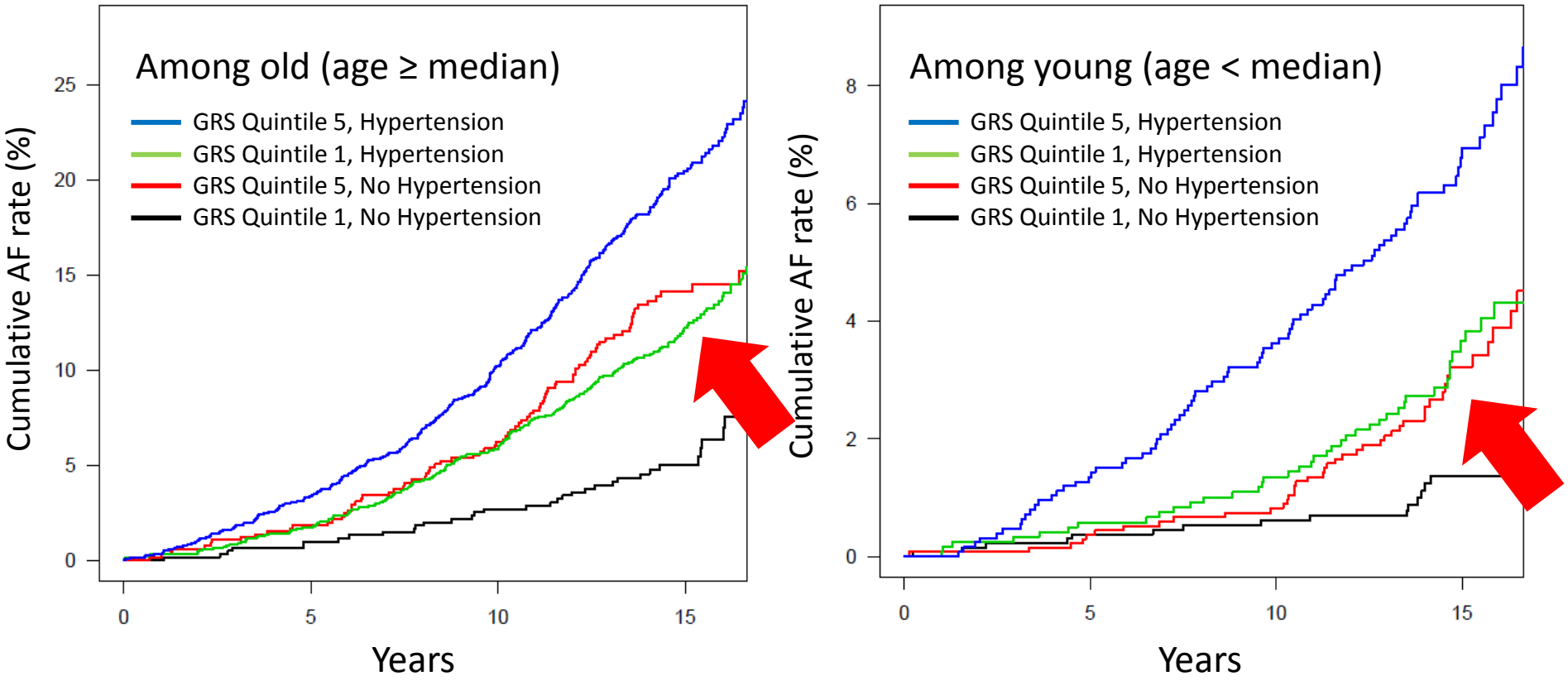


Cumulative incident atrial fibrillation events according to AF-GRS.
Dotted lines indicate 95% CI the cumulative event rate estimate.

Tada H, Ellinor PT, Kathiresan S, et al. ***Stroke.*** 2014;45:2856-62.

AF-genetic risk score (GRS) is equivalent with hypertension for risk of future AF event

Cumulative AF events according to median age, AF-GRS quintile, and hypertension



A low AF-GRS and hypertension ≈ A high GRS but without hypertension

Tada H, Ellinor PT, Kathiresan S, et al. ***Stroke.*** 2014;45:2856-62.

Summary

◆ On considering the role of anticoagulants, we should care of risk stratification including genetic factors as well as underlying diseases.

◆ For example, the AF-GRS comprising 12 SNPs which were equivalent to “Hypertension” was associated with incident atrial fibrillation and ischemic stroke.

◆ Awareness of the risk, correction of reversible risk factors, and tailored oral anticoagulation are at present the best tools to improve stroke prevention and avoid major bleeding in atrial fibrillation particularly in elderly patients.

How to get to Kanazawa

Seoul

Kanazawa

Busan

Tokyo

Osaka

Fukuoka

Acknowledment

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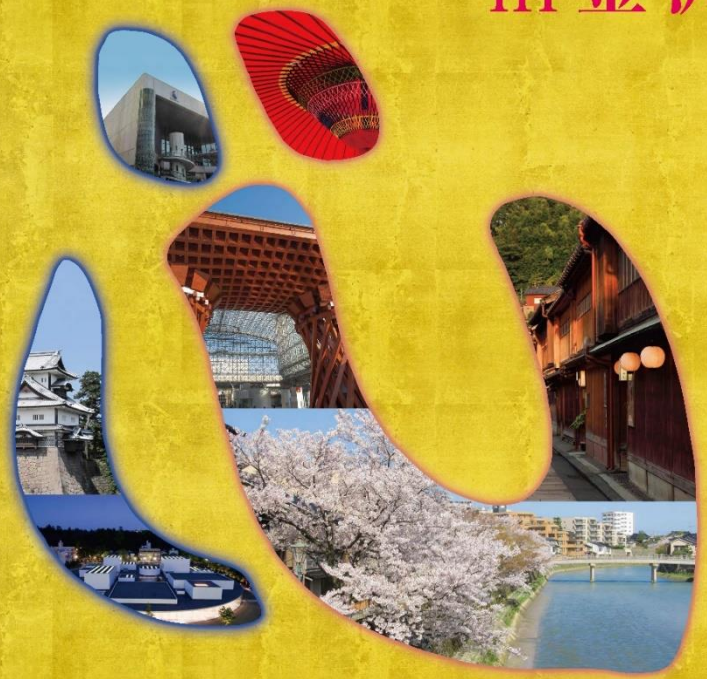
The 81st Annual Scientific Meeting of the Japanese Circulation Society
in 金沢



会期：2017年3月17(金)▲19(日)

会場：石川県立音楽堂 他

JCS2017

会長：山岸 正和
（金沢大学臓器機能制御学・循環器内科）

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The 81st Annual Scientific Meeting of the Japanese Circulation Society

March 17 (Fri)-19 (Sun), 2017 in Kanazawa, Japan

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