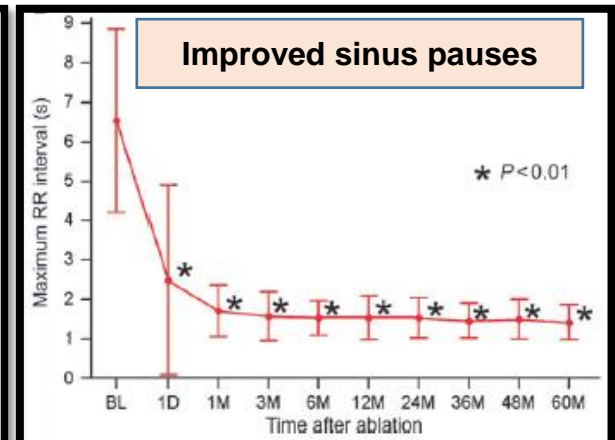
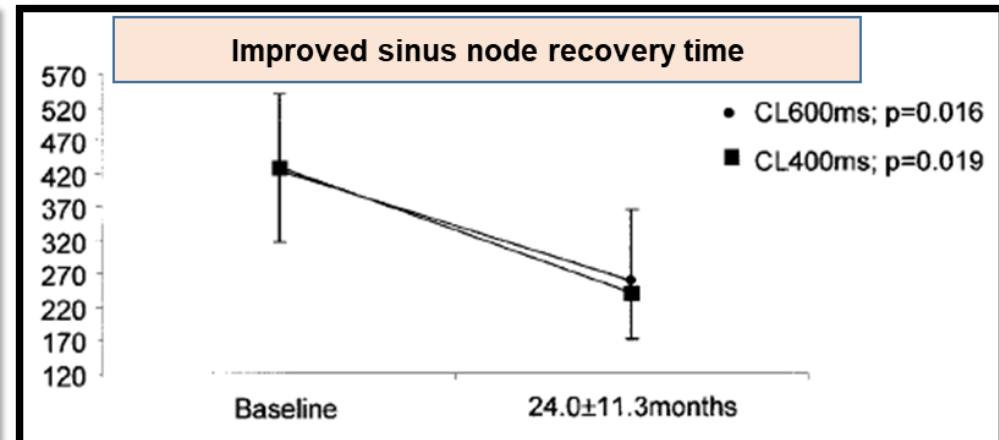
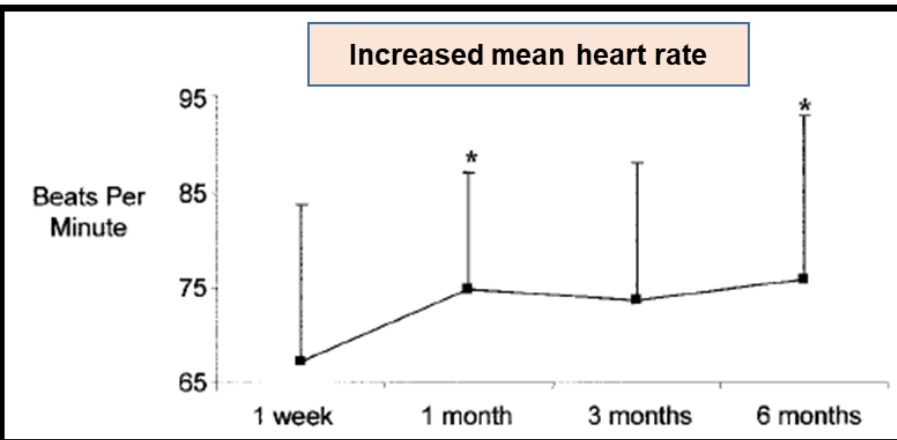


# **Genetic background of sinus node dysfunction requiring permanent pacemaker implantations after atrial fibrillation catheter ablation**

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# Introduction



● AF catheter ablation improves the sinus node dysfunction as evidenced by an increased heart rate, improved sinus pauses, and improved sinus node recovery times.

# Introduction

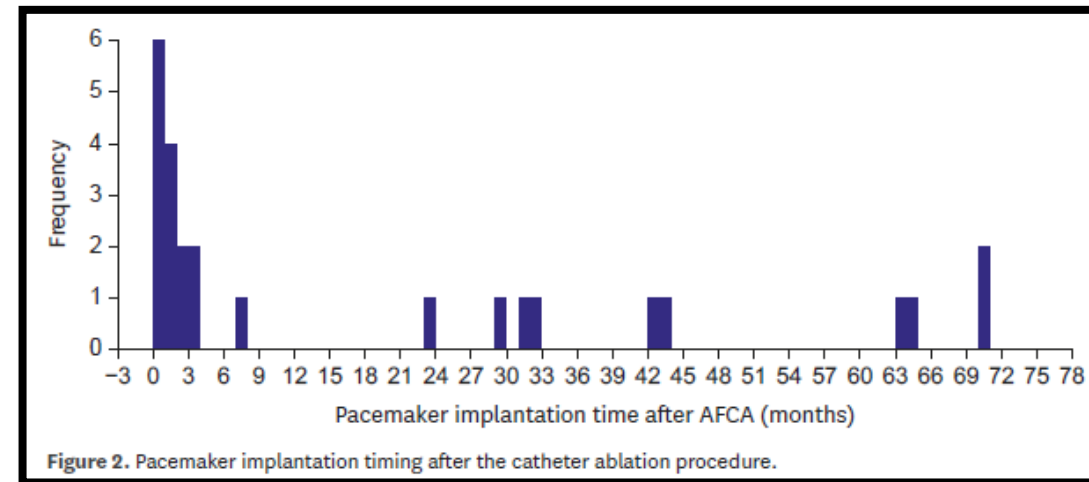
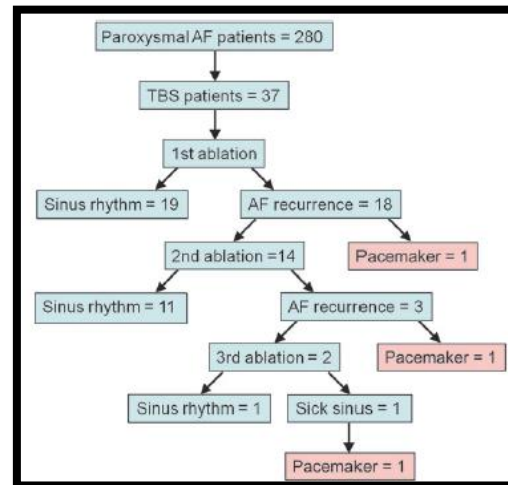
AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation. <sup>B16–B18</sup>

Ila

C

- AF catheter ablation can be considered to avoid a pacemaker implantation in AF-related bradycardia or sinus pauses after AF conversion (class IIA but level of C in current guidelines).

2020 ESC guideline for AF



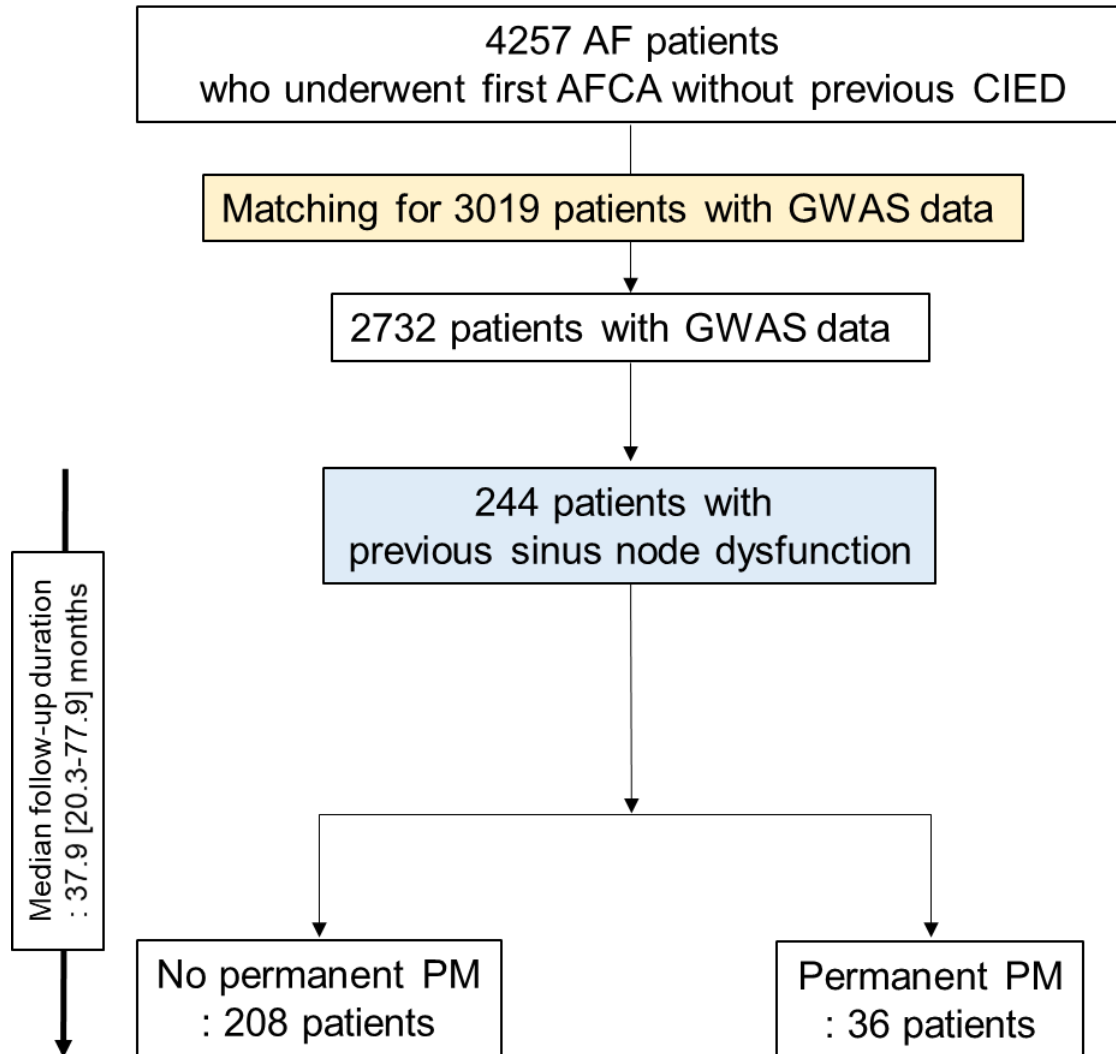
- A permanent pacing rhythm is still needed during the long-term period after AFCA.
- 8% with permanent PM in Inada et al. 11.3% with permanent PM in Hwang et al.

# Purpose

- Intrinsic or pre-existing SND, genetic polymorphism, might contribute to permanent PM implantations during long-term follow-up periods after AF catheter ablation.
- We aimed to identify single-nucleotide polymorphisms associated with permanent PM implantations after AF catheter ablation in patients with AF and SND.
- We aimed to develop and compare the clinical and genetic risk model to predict the risk of a permanent PM implantation after AF catheter ablation.

# Methods

## : Study flow chart



- SND was defined as symptomatic sinus bradycardia (under < 50 bpm) or sinus pauses longer than 3 s with or without low-dose antiarrhythmic drugs to maintain sinus rhythm.

- CPVI: all patients
- CTI ablation: 88.9% of patients, routinely performed
- Other linear ablation: 69.8% of the patients at the operator's discretion

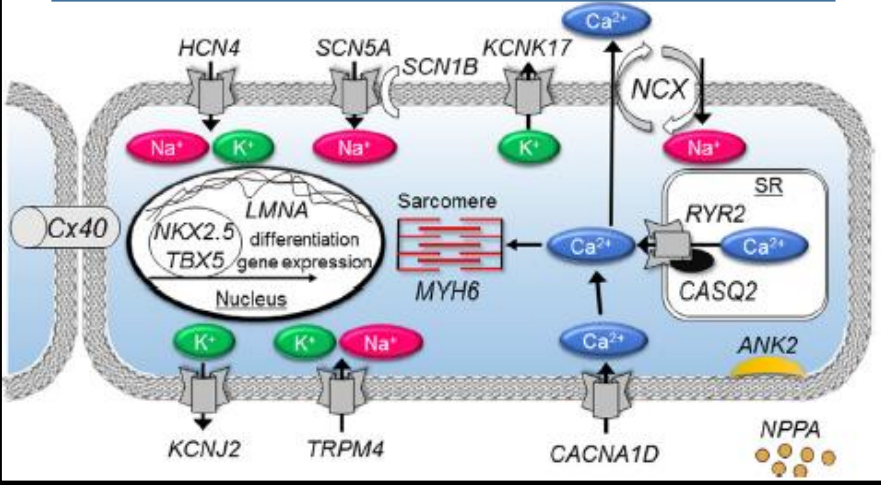
# Methods

## : GWAS data

Ishikawa T. et al. *J Arrhythm* 2016;32:352-8

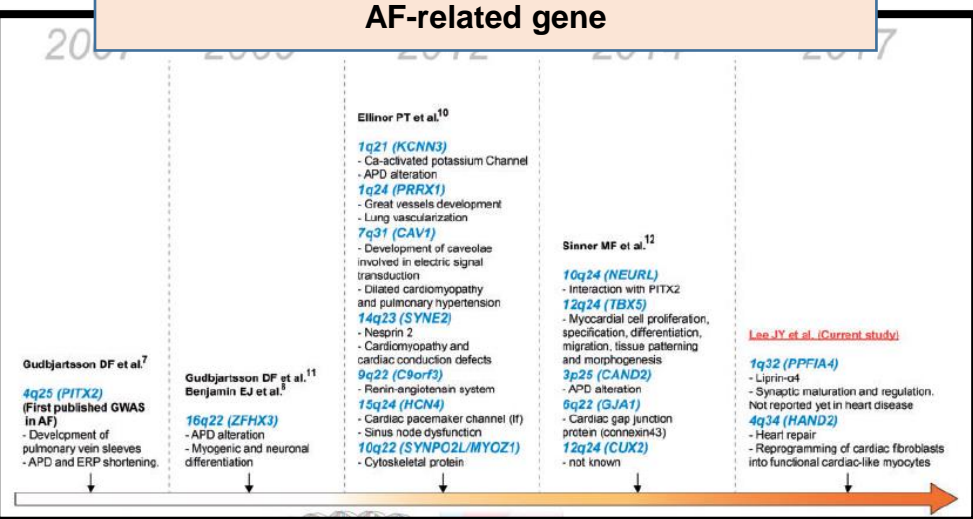
Lee JY. et al. *Eur Heart J* 2017;38:2586-94

### Inherited bradyarrhythmia-related gene



- QuickGene DNA whole blood kit with a QuickGene mini 80 for extracting genome DNA for peripheral blood
- The Axiom Precision Medicine Research Array (PMRA) for DNA genotyping data

### AF-related gene



238 SNPs

SNPs	Nearest gene	SNPs	Nearest gene
rs4074536	CASQ2	rs11154022	GJA1
rs6666258	KCNN3	rs11154027	GJA1
rs13376333	KCNN3	rs9320841	GJA1
rs11129795	SCN5A	rs1015451	GJA1
rs1805126	SCN5A	rs3807989	CAV1
rs12053903	SCN5A	rs11773845	CAV1
rs3922844	SCN5A	rs116996231	FBP1
rs11708996	SCN5A	rs10512236	C9orf3
rs45567533	SCN5A	rs10821415	C9orf3
rs9851724	SCN10A	rs883079	TBX5
rs7633988	SCN10A	rs3825214	TBX5
rs6795970	SCN10A	rs7312625	TBX5
rs6801957	SCN10A	rs7135659	TBX5
rs7433306	SCN10A	rs1895585	TBX5
rs6800541	SCN10A	rs1896312	TBX3
rs10428132	SCN10A	rs365990	MYH6
rs6798015	SCN10A	rs452036	MYH6
rs17042171	PITX2	rs1152591	SYNE2
rs2200733	PITX2	rs7164883	HCN4
rs6843082	PITX2	rs1858800	ZFH3
rs10033464	PITX2	rs7193343	ZFH3
rs3853445	PITX2	rs2106261	ZFH3

# Results

## : Baseline characteristics

	Overall (n=244)	No PPM (n=208)	PPM (n=36)	p- value
Age, years	65.0 [59.0, 72.0]	65.0 [57.5, 71.0]	67.5 [61.5, 75.0]	0.152
Male, n	142 (58.2%)	116 (55.8%)	26 (72.2%)	0.096
Paroxysmal AF, n	194 (79.5%)	167 (80.3%)	27 (75.0%)	0.616
Body mass index, kg/m <sup>2</sup>	24.3 [22.7, 26.0]	24.1 [22.5, 25.9]	25.5 [23.9, 26.9]	0.013
CHA <sub>2</sub> DS <sub>2</sub> VASc score	2.0 [1.0, 3.0]	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	0.892
Congestive heart failure, n	25 (10.2%)	23 (11.1%)	2 (5.6%)	0.479
Hypertension, n	126 (10.2%)	107 (51.4%)	19 (52.8%)	>0.999
Diabetes mellitus, n	32 (13.1%)	24 (11.5%)	8 (22.2%)	0.137
Stroke/TIA, n	36 (14.8%)	30 (14.4%)	6 (16.7%)	0.924
Vascular disease, n	28 (11.5%)	21 (10.1%)	7 (19.4%)	0.180
LA dimension, mm	41.0 ± 6.2	40.6 ± 6.1	43.6 ± 6.1	0.006
LA volume index, mL/m <sup>2</sup>	36.1 [28.4, 44.4]	36.0 [28.4, 43.2]	38.2 [30.1, 47.0]	0.346
LVEF, %	65.0 [61.0, 69.2]	65.0 [61.0, 69.0]	66.5 [62.5, 70.0]	0.413
Eem	10.6 [8.0, 13.0]	10.6 [8.0, 13.0]	11.3 [8.5, 14.7]	0.138

	Overall (n=244)	No PPM (n=208)	PPM (n=36)	p-value
CT LA volume index	80.2 [66.9, 99.3]	79.8 [66.7, 99.6]	84.0 [69.3, 96.7]	0.989
Mean LA wall thickness, mm	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.4	0.679
Pericardial fat volume, cm <sup>3</sup>	110.1 [79.6, 136.0]	111.7 [79.2, 136.3]	100.6 [80.5, 124.3]	0.415
Ablation character				
Extra-PV linear ablation, n	169 (69.8%)	143 (69.4%)	26 (72.2%)	0.887
CTI ablation, n	217 (88.9%)	182 (87.5%)	35 (97.2%)	0.153
Extra-PV triggers, n	21 (11.7%)	17 (11.0%)	4 (15.4%)	0.758
Mean LA voltage, mV	1.3 [0.8, 1.9]	1.3 [0.8, 1.9]	1.4 [1.1, 1.9]	0.443
Post-AFCA medication, n				
Beta blocker at discharge	56 (23.0%)	45 (21.6%)	11 (30.6%)	0.337
AAD at discharge	33 (13.5%)	28 (13.5%)	5 (13.9%)	>0.999

# Results

: SNPs related high risk for permanent PM after AFCA

SNPs	Nearest gene	SNPs	Nearest gene
rs4074536	CASQ2	rs11154022	GJA1
rs666258	KCNN3	rs11154027	GJA1

SNPs related to high risk for permanent PM after AFCA

SNPs	Nearest Gene	Chromosome	Position	Minor/ Major allele	Risk/ Reference allele	Phenotype	Odds ratio (95% CI)	p-value*
rs3922844	SCN5A	3	38624253	T/C	T/C	PR interval, QRS duration	3.24 (1.51-6.96)	0.003
rs9320841	GJA1	6	122114451	G/A	G/A	Resting heart rate	1.98 (1.17-3.34)	0.011
rs1015451	GJA1	6	122131485	C/T	C/T	Heart rate	1.72 (1.01-2.93)	0.046

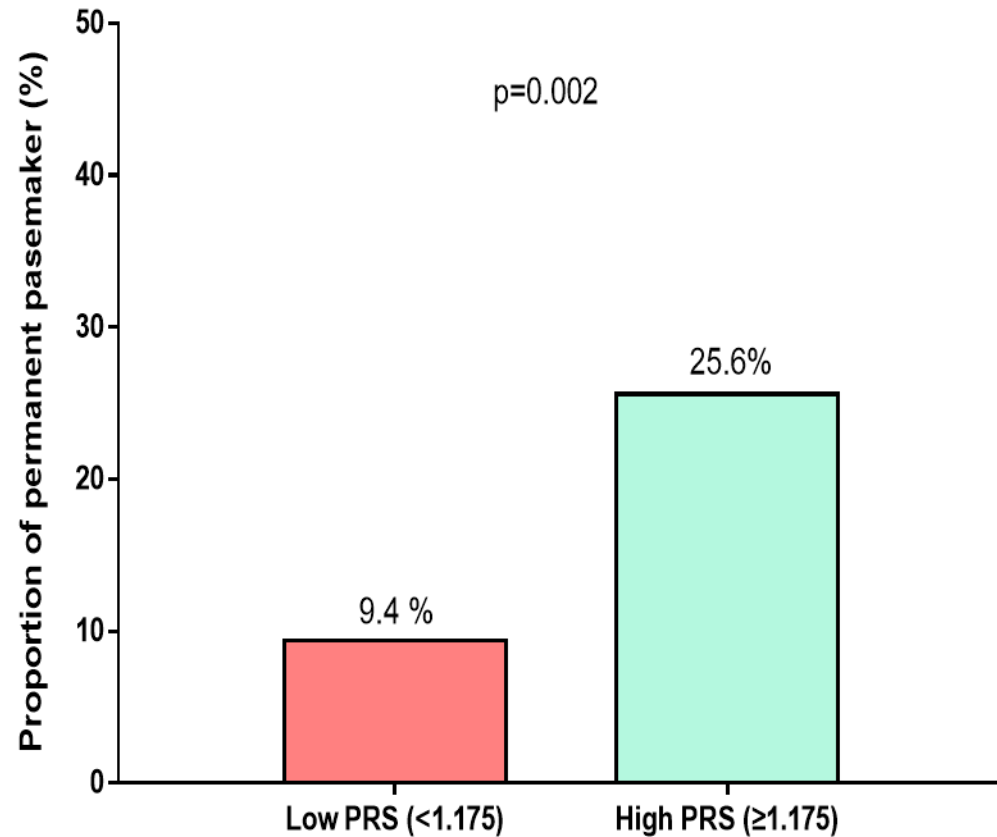
rs17042171	PITX2	rs1152591	SYNE2
rs2200733	PITX2	rs7164883	HCN4
rs6843082	PITX2	rs1858800	ZFHX3
rs10033464	PITX2	rs7193343	ZFHX3
rs3853445	PITX2	rs2106261	ZFHX3



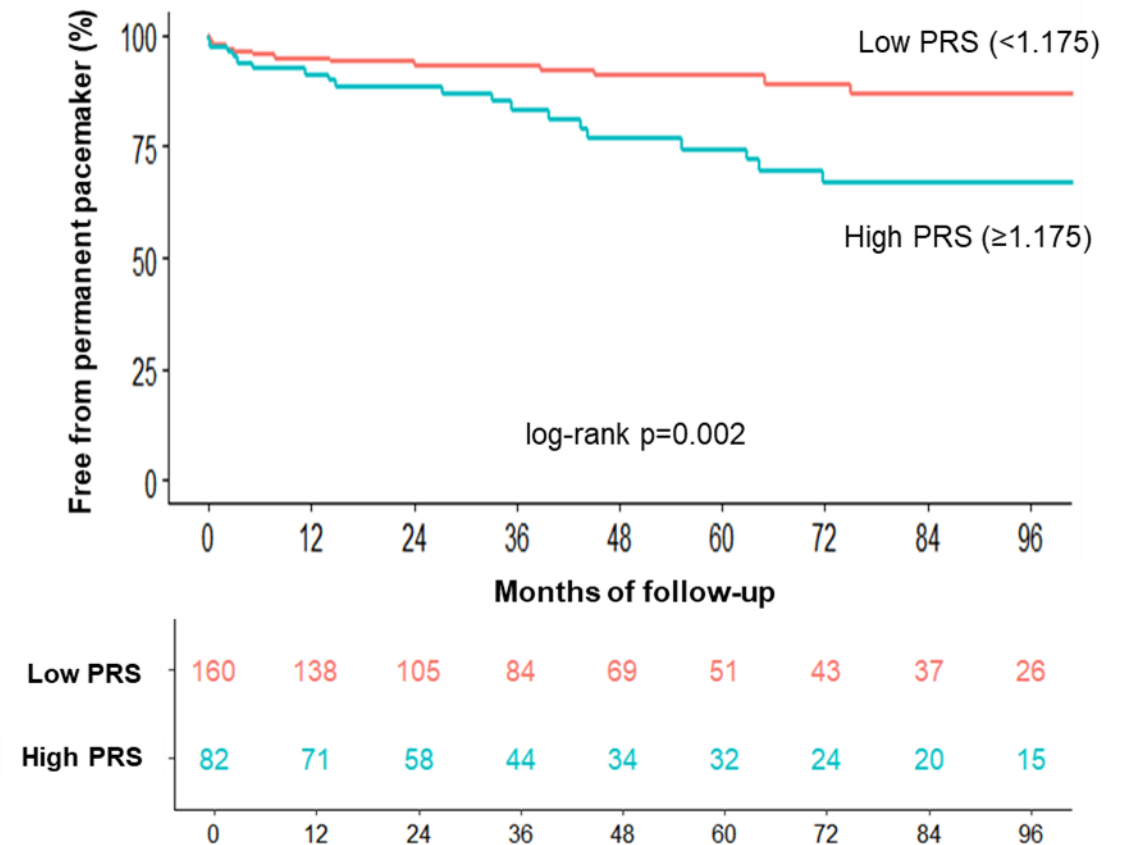
# Results

: PRS related to high risk for permanent PM after AFCA

A. Rate of pacemaker implantation according to PRS group



B. Kaplan-Meier curve for pacemaker implantation by PRS group



# Results

## : Cox regression analysis

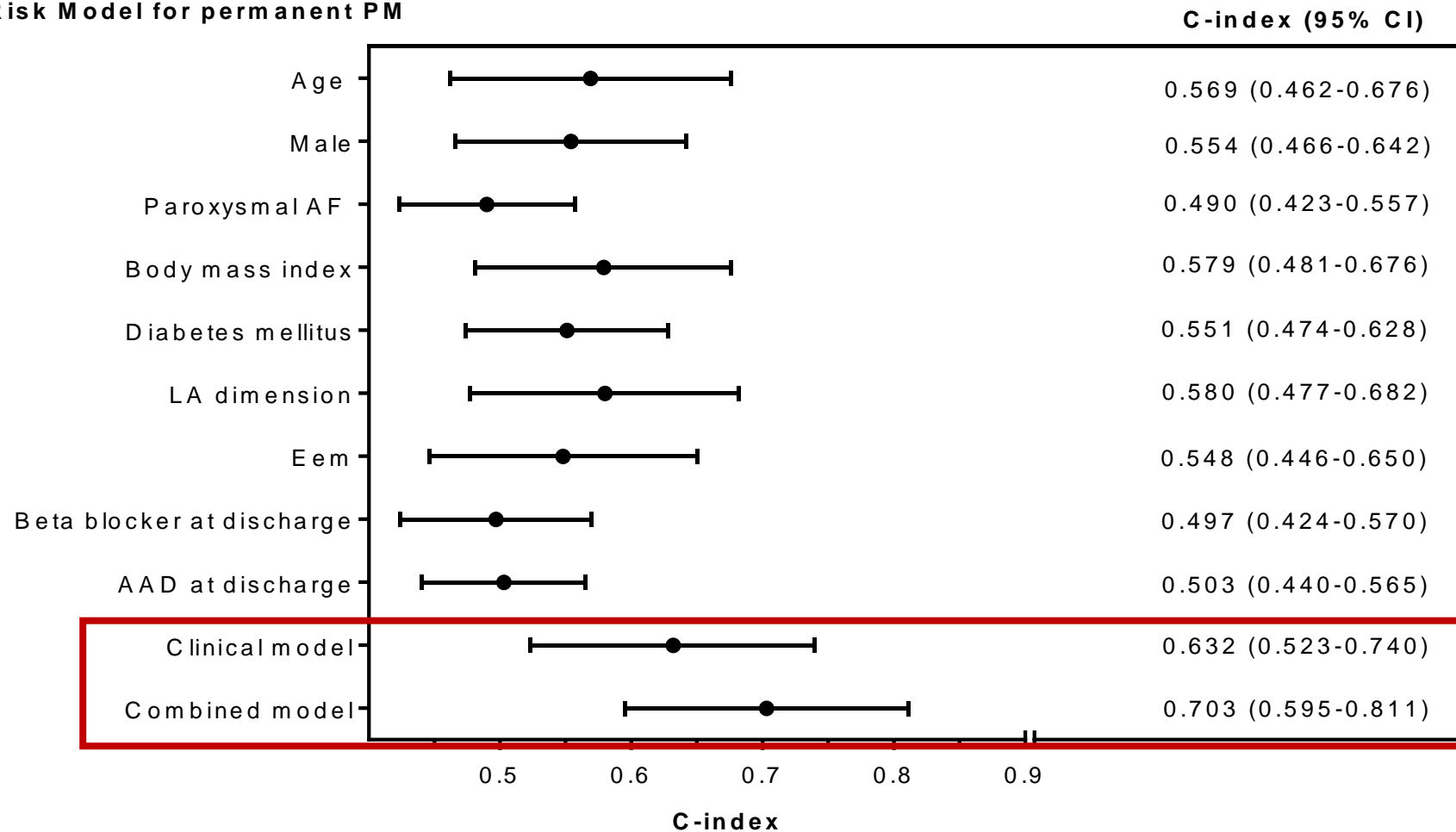
	Univariable model		Multivariable model	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.03 (0.99-1.07)	0.131	1.06 (1.02-1.12)	0.008
Male	2.03 (0.98-4.22)	0.058	2.81 (1.26-6.29)	0.012
Paroxysmal AF	0.83 (0.39-1.77)	0.627	0.99 (0.39-2.52)	0.989
Body mass index	1.08 (0.98-1.20)	0.102	1.05 (0.93-1.20)	0.435
CHA <sub>2</sub> DS <sub>2</sub> VASc score	1.01 (0.81-1.24)	0.956		
Congestive heart failure	0.60 (0.14-2.53)	0.490		
Hypertension	0.93 (0.48-1.78)	0.817		
Diabetes mellitus	1.61 (0.73-3.58)	0.240	1.34 (0.56-3.21)	0.510
Stroke/TIA	1.10 (0.46-2.64)	0.838		
Vascular disease	1.38 (0.60-3.17)	0.441		
LA dimension	1.06 (1.01-1.11)	0.028	1.05 (0.97-1.13)	0.232
LA volume index	1.01 (0.98-1.03)	0.509		
LVEF	1.00 (0.96-1.04)	0.894		
Eem	1.04 (0.98-1.12)	0.202	1.02 (0.94-1.11)	0.664

	Univariable model		Multivariable model	
	HR (95% CI)	P-value	HR (95% CI)	P-value
CT LA volume index	1.00 (0.98-1.01)	0.723		
Mean LA wall thickness	1.00 (0.36-2.79)	0.996		
Pericardial fat volume	1.00 (0.99-1.00)	0.451		
Ablation character				
Extra-PV linear ablation	0.98 (0.47-2.05)	0.966		
CTI ablation	2.79 (0.38-20.54)	0.313		
Extra-PV triggers	1.60 (0.55-4.66)	0.387		
Mean LA voltage	1.32 (0.78-2.25)	0.302		
Post-AFCA medication				
Beta blocker at discharge	1.41 (0.70-2.87)	0.339	1.00 (0.47-2.13)	0.998
AAD at discharge	1.25 (0.48-3.23)	0.645	0.93 (0.31-2.84)	0.903
GWAS data				
Polygenic risk score	2.18 (1.41-3.37)	<0.001	2.56 (1.60-4.11)	<0.001

# Results

: Clinical and Genetic risk model for predicting permanent PM after AFCA

Risk Model for permanent PM



} P-value < 0.001

# Summary and Conclusions

- In AF patients with SND, 15% eventually underwent permanent pacemaker implantation.
- Rs3922844 near SCN5A and rs9320841 and rs1015451 near GJA1 were risk SNPs for pacemaker implantation after AF catheter ablation
- Addition of the polygenic risk score to the clinical risk model improved prediction power for pacemaker implantation after AF catheter ablation.
- In addition to clinical risk factors, genetic polymorphisms could be considered in patients with AF with SND before AF ablation and a permanent pacing rhythm.



**Thank you for your attention**

