Prediction of Atrial Fibrillation Using Exercise-/ Holter-Based Electrocardiogram

Kyoung-Min Park, MD PhD

Division of Cardiology, Department of Medicine
Heart Vascular Stroke Institute
Samsung Medical Center, Sungkyunkwan University School of Medicine

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Exercise Induced Frequent Atrial Premature Complexes : A Potent of Atrial Fibrillation

Jin Kyung Hwang, Seung-Jung Park, Young Keun On,
June Soo Kim, Kyoung-min Park

Cardiac & Vascular Center, Samsung Medical Center,
Sungkyunkwan University School of Medicine

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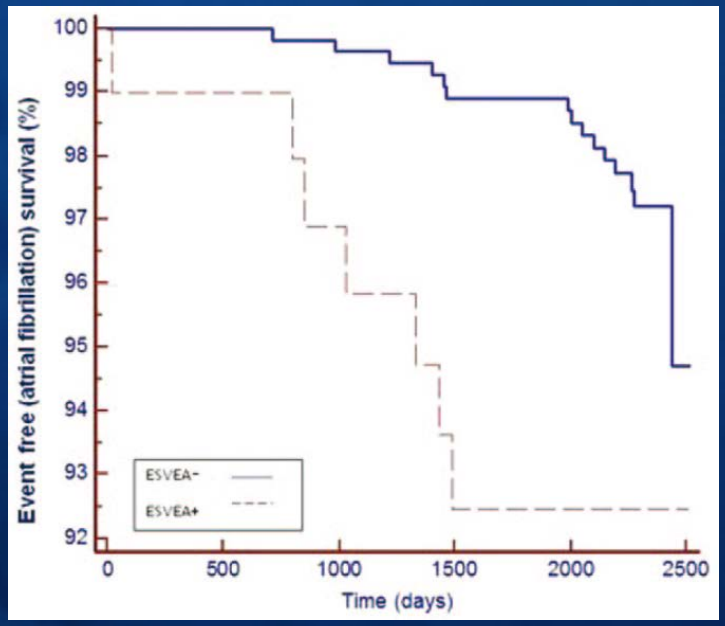
Backgrounds

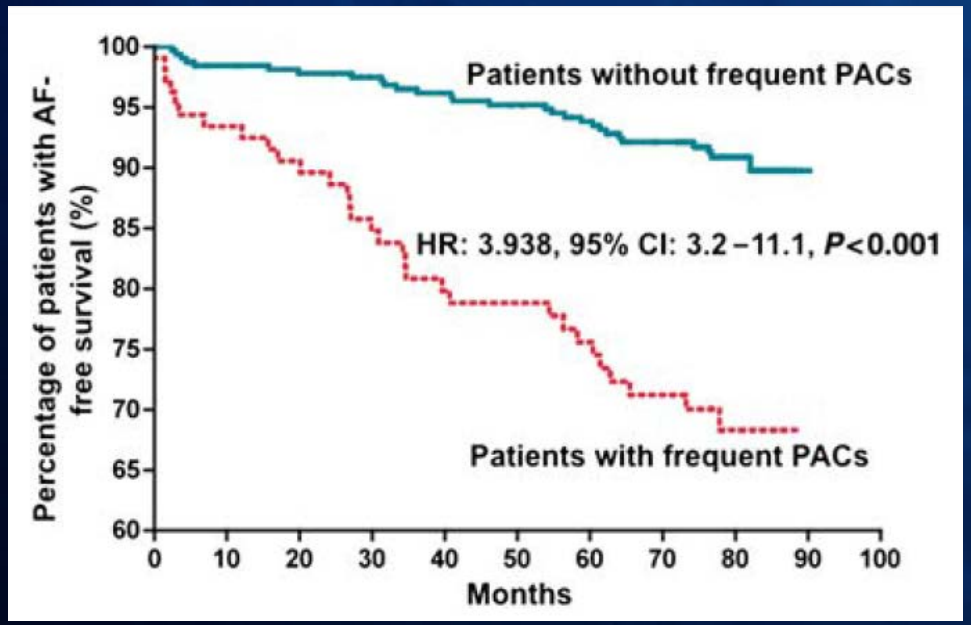
- Atrial fibrillation (AF) is the most common arrhythmia in the elderly.
- Its prevalence is estimated at 8.6% in Medicare beneficiaries and doubles with each advancing decade of life. [1-2)]
- AF is highly associated with increased risk of death, stroke, and congestive heart failure.[3)]

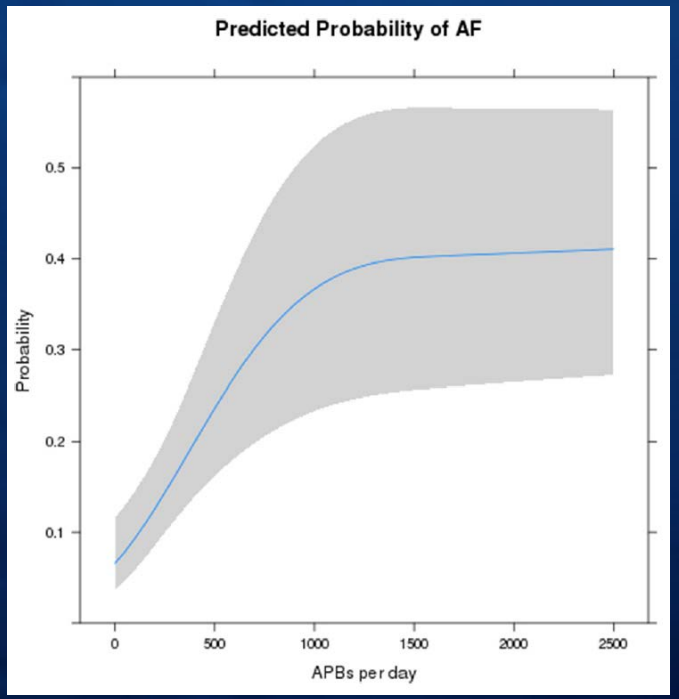


1) Circ Cardiovasc Qual Outcomes. 2012;5:85-93, 2) Am J Cardiol. 1998;82:2N-9N, 3) JAMA. 2001;285:2370-5

Backgrounds

- Atrial premature complexes (APCs) shown to trigger paroxysmal AF, they are, at present, considered innocuous and generally left untreated.
- However, excessive APCs increase risk of AF and stroke.[1-3)]





1) Circulation. 2010;121:1904-11,
2) Europace. 2012;14:942-7, 3) Stroke. 2015;46:936-41.

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Backgrounds

- Frequent APCs might cause atrial remodeling near the SA nodal area and contribute to development of AF.[1)]
- Increased atrial vulnerability in patient with AF permits repetitive atrial responses by APCs to induce atrial fibrillation.[2)]
- However, clinical implication of frequent APCs during exercise is unclear.

1) Europace. 2013;15:205-11, 2) Josephson's Clinical Cardiac Electrophysiology, 5th edition, Ch 9.

Study Aim

We investigated the association between frequent APCs during Treadmill exercise test (TMT) and AF.

1) Europace. 2013;15:205-11

Methods

- From Jan. 2013 to Dec. 2014 in SMC
- TMT protocol : standard Bruce protocol
- Rate slowing medication : discontinue 3 days before exam.
- Target HR = (220 – age) x 0.85

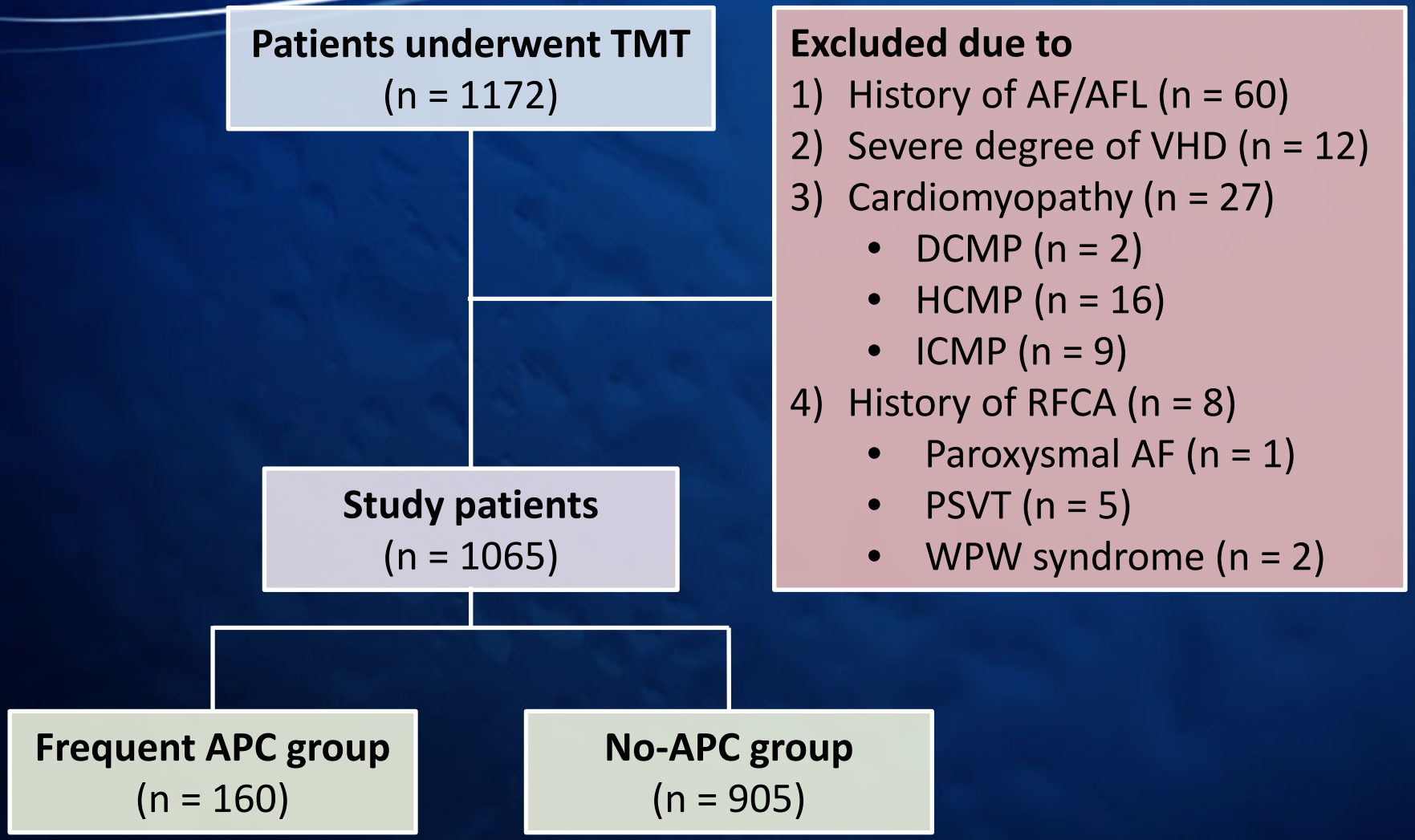
- Frequent APCs
  - ≥ 5 APCs per stage (d/t 5.3 ± 6.4 beats/stage)

- Chronotropic incompetence (CI)
  - Maximal HR/Age-predicted maximal HR (220-age) <0.8

Methods

- Inclusion
  - Age ≥20 years
  - Consecutive patients undergoing TMT
- Exclusion
  - History of AF/AFL
  - Valvular heart disease
  - Cardiomyopathy
  - History of RFCA
- Primary outcome
  - Newly detected AF after TMT test
  - Include AF/AFL and AT running more than 30 sec

Methods



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Results

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Baseline: demographic, PMHx

	APC group (n = 160)	No-APC group (n = 905)	P value
Male	106 (66%)	580 (64%)	0.60
Age (years)	**57 ± 10**	**53 ± 12**	**<0.01**
BMI (kg/m²)	25 ± 3	24 ± 3	0.06
Smoker	22 (14%)	143 (16%)	0.80
DM	21 (13%)	158 (18%)	0.18
HTN	71 (44%)	368 (41%)	0.38
CVA	9 (6%)	31 (3%)	0.18
Dyslipidemia	54 (34%)	346 (38%)	0.28
Prior MI	**2 (1%)**	**59 (7%)**	**0.01**
Prior PCI	**12 (8%)**	**181 (20%)**	**<0.01**
Prior CABG	1 (1%)	15 (2%)	0.32

Values are mean ± SD or n (%). Abbreviations: BMI=body mass index; DM=diabetes mellitus; HTN=hypertension; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft surgery

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Baseline: medication, TTE

	APC group (n = 160)	No-APC group (n = 905)	P value
Beta-blockers	21 (13%)	142 (16%)	0.41
DHP-CCB	14 (9%)	60 (7%)	0.33
Non-DHP-CCB	9 (6%)	39 (4%)	0.46
ACEi/ARB	30 (19%)	189 (21%)	0.54
Statin	**33 (21%)**	**283 (31%)**	**0.01**
LVEF (%)	64 ± 6	64 ± 7	0.40
LA size (mm)	**40 ± 7**	**38 ± 12**	**<0.1**
LAVI (mL/m^2)	**38 ± 18**	**30 ± 9**	**<0.1**

Values are mean ± SD or n (%). Abbreviations: DHP-CCB=dihydropyridine calcium channel blocker; Non-DHP-CCB=non-dihydropyridine calcium channel blocker; ACEi/ARB=angiotensin converting enzyme inhibitor or aldosterone receptor blocker; LVEF=left ventricular ejection fraction; LA size=left atrial size measure by M-mode at PSAX; LAVI=left atrial volume index measure by bi-plan method

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Baseline: TMT

	APC group (n = 160)	No-APC group (n = 905)	P value
Rest HR	79 ± 15	80 ± 14	0.89
Rest SBP	125 ± 18	123 ± 18	0.26
Rest DBP	78 ± 14	77 ± 11	0.10
Target HR	**139 ± 8**	**142 ± 10**	**<0.01**
Maximal HR	**166 ± 25**	**161 ± 24**	**0.02**
Maximal SBP	**185 ± 25**	**179 ± 29**	**0.01**
Maximal DBP	**83 ± 17**	**78 ± 15**	**<0.01**
Total exercise time	10 ± 2	10 ± 2	0.26
Total METs	12 ± 2	12 ± 2	0.79
Chronotropic incompetence	9 (6%)	85 (9%)	0.12

Values are mean ± SD or n (%). Abbreviations: HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MET=metabolic equivalents

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Arrhythmia Outcomes

- Follow up duration : median 1 (IQR: 0.1-1.8) year

	APC group (n = 160)	No-APC group (n = 905)	P value
Newly detected AF	**9 (6%)**	**4 (0.4%)**	**<0.01**
NSVT	1 (0.6%)	4 (0.4%)	0.56
Stroke	-	6 (0.7%)	0.60
Diagnosis of CAD	10 (6%)	29 (3%)	0.07

Values are n (%). Abbreviations: AF/AFL=atrial fibrillation or flutter; NSVT=non-sustained ventricular tachycardia; CAD=coronary artery disease

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Independent risk factor for AF

	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Male	0.5 (0.2-2.0)	0.35	-	-
Age	1.0 (1.0-1.1)	0.65	-	-
BMI	1.0 (0.8-1.2)	0.78	-	-
HTN	0.6 (0.2-2.1)	0.45	-	-
Prior MI	0.0 (0.0-N/A)	0.99	-	-
Prior PCI	0.0 (0.0-N/A)	0.99	-	-
LAVI	1.0 (1.0-1.1)	0.05	-	-
Chronotropic incompetence	**12.9 (4.3-38.4)**	**<0.01**	**25.4 (7.0-50.9)**	**<0.01**
Frequent APCs	**13.4 (4.0-34.2)**	**<0.01**	**24.2 (6.4-45.5)**	**<0.01**

Adjusted covariates were age, male, LAVI, maximal HR, and frequent APCs. Abbreviations: OR=odd ratio; CI=confidence interval; BMI=body mass index; MI=myocardial infarction; PCI=percutaneous coronary intervention; LAVI=left atrial volume index; CI=chronotropic incompetence; TMT=treadmill test.

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Summary

- In APC group,
  - Age was older than that of no-APC group.
  - LAVI was larger than that of no-APC group.
  - New onset AF was more reported.

- Independent predictors for newly detected AF
  - Chronotropic incompetence and frequent APCs during TMT was significantly associated with new onset AF.
  - The results were consistent after multiple adjustment.

Conclusions

- Excessive APCs are no more benign.
- Frequent APCs during exercise may be a predictive factor of detection of AF.
- Closed monitoring for further AF progression in these patients will be needed.
- We need large and well-designed prospective study to confirm the study results.

Long-term Outcomes of the Patients with Frequent Atrial Premature Contractions : Results from Retrospective Single Center Study

Kwang Jin Chun, Jin Kyung Hwang, Seung-Jung Park, Young Keun On, June Soo Kim, Kyoung-Min Park

Cardiac & Vascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine

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Background

- Atrial Premature Contractions (APCs) are generally considered benign

- Some studies indicate that APCs often precede or forewarn of a cardiovascular diseases, including arrhythmia, in healthy individuals

Ann Intern Med.2013;159:721-728
PLOS ONE 2013;8:1-7
Eur Neurol 2009;61:285-288
Asian Cardiovascular & Thoracic Annals 2014
Europace 2013;14:941-947

- However, it remains unclear whether frequent APCs can predict adverse cardiovascular events such as ischemic stroke, cardiomyopathy, AF, and death

- The aim of this study is to clarify the role of frequent APCs in predicting death, stroke, cardiovascular events among out-patients clinic in a single center using retrospectively long-term follow-up data.

Subjects and Methods

- Study population
  - Jan. 1994 – Dec. 2002, diagnosed with APCs, more than 100 beats/ day during Holter monitoring, were enrolled in this study
  - Outpatients clinic, Samsung medical center
  - The patients who had structural heart disease or significant arrhythmias, atrial fibrillation or atrial flutter, before the initial Holter monitoring were all excluded.
  - All enrolled patients were sub-grouped into four according to the proportion of daily APCs burden:
  - Group (Gp) 1 (APCs/day ≤ 5000)

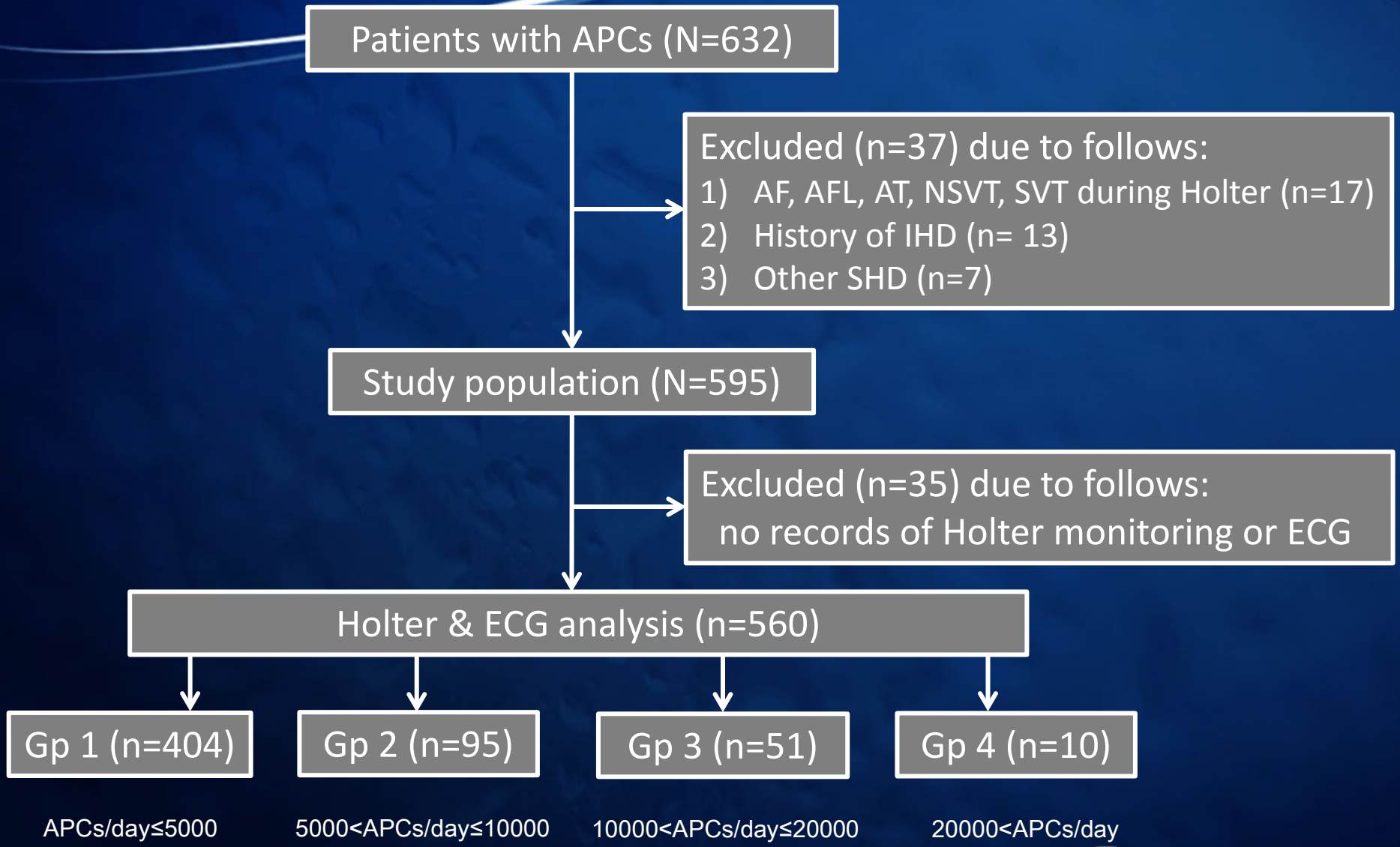
    Gp 2 (5000 < APCs/day ≤ 10000)

    Gp 3 (10000 < APCs/day ≤ 20000)

    Gp 4 (20000 < APCs/day)
  - The association between APCs burden and various outcomes were assessed using Cox proportional hazard models

TTE: transthoracic echocardiography, AF: atrial fibrillation, AFL: atrial flutter, AT: atrial tachycardia, NSVT: non-sustained ventricular tachycardia, SVT: sustained ventricular tachycardia

Subjects and Methods



Results 1. Baseline Characteristics

- Mean follow-up: 11.4±3.0 years

	Gp 1 (n=404)	Gp 2 (n=95)	Gp 3 (n=51)	Gp 4 (n=10)	P value
Sex, n (%)					0.69
Male	223 (55.2)	58 (61.1)	30 (58.8)	7 (70.0)	
Age (yo)	60.6 ± 14.3	59.8 ± 15.7	60.4 ± 14.5	66.5 ± 10.6	0.54
Height (cm)	162.3 ± 8.7	162.5 ± 10.3	163.2 ± 9.0	165.7 ± 13.7	0.61
Weight (kg)	62.9 ± 11.0	63.3 ± 10.8	64.2 ± 10.4	62.0 ± 12.4	0.83
APC burden (n/24hrs)	1909 ± 1270	6985 ± 1351	13749 ± 2636	25815 ± 4604	<0.001
VPC burden (n/24hrs)	3131±2627	1196±2699	2904±5888	2774±1080	0.92
Mean f/u period (yo)	11.7±3.8	12.1±3.2	12.9±3.3	10.1±2.9	0.39
Medical History					
DM, n (%)	88 (21.8)	16 (16.8)	9 (17.6)	0 (0.0)	0.28
HTN, n (%)	197 (48.8)	39 (41.1)	22 (43.1)	6 (60.0)	0.43
Dyslipidemia, n (%)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.75

Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test.
APC, atrial premature complexes; DM, diabetes mellitus; HTN, hypertension
VPC, ventricular premature complexes; n, numbers; yo, years old

Results 1. Baseline Characteristics

	Gp 1 (n=404)	Gp 2 (n=95)	Gp 3 (n=51)	Gp 4 (n=10)	P value
Symptom, n (%)					
Palpitation	147 (36.4)	34 (35.8)	17 (33.3)	5 (50.0)	0.85
Chest pain	108 (26.7)	26 (27.4)	18 (35.3)	0 (0.0)	0.13
Dyspnea	82 (20.3)	22 (23.2)	14 (27.5)	4 (40.0)	0.43
Dizziness	76 (18.8)	24 (25.3)	6 (11.8)	1 (10.0)	0.17
Syncope	49 (12.1)	6 (6.3)	0 (0.0)	0 (0.0)	0.01
Fatigue	6 (1.5)	1 (1.1)	2 (3.9)	0 (0.0)	0.56

Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test.
APC, atrial premature complexes; VPC, ventricular premature complexes; yo, years old

Results 2. Echocardiographic Parameters

	Gp 1 (n=404)	Gp 2 (n=95)	Gp 3 (n=51)	Gp 4 (n=10)	P value
EchoCG parameters					
LVEDD (mm)	50.4 ± 6.2	50.4 ± 7.2	51.6 ± 6.5	54.9 ± 7.3	0.09
LVESD (mm)	31.5 ± 6.9	32.2 ± 6.9	33.2 ± 7.7	33.2 ± 10.7	0.37
LVEF (%)	60.9 ± 10.1	59.3 ± 9.7	58.8 ± 10.9	63.7 ± 16.1	0.26
LVPWd (mm)	9.0 ± 1.9	9.0 ± 1.5	9.2 ± 1.3	8.6 ± 1.2	0.76
LVSd (mm)	9.3 ± 3.6	9.1 ± 1.8	9.4 ± 1.5	8.6 ± 1.1	0.84
LA size (mm)	**37.7 ± 6.4**	**39.6 ± 7.8**	**39.8 ± 5.5**	**42.0 ± 4.6**	**0.08**

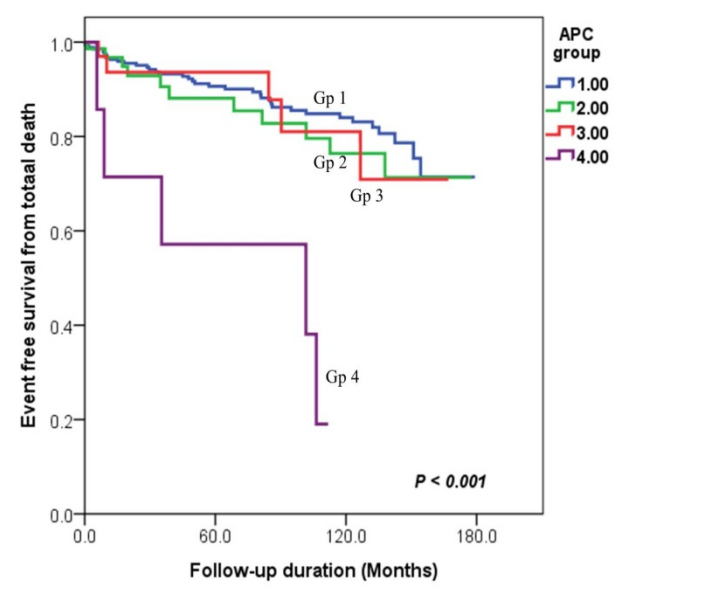
Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test.
LV, left ventricle; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LVEF, LV ejection fraction; LVPWd, LV posterior wall dimension; LVSd, LV septal dimension; LA, left atrium

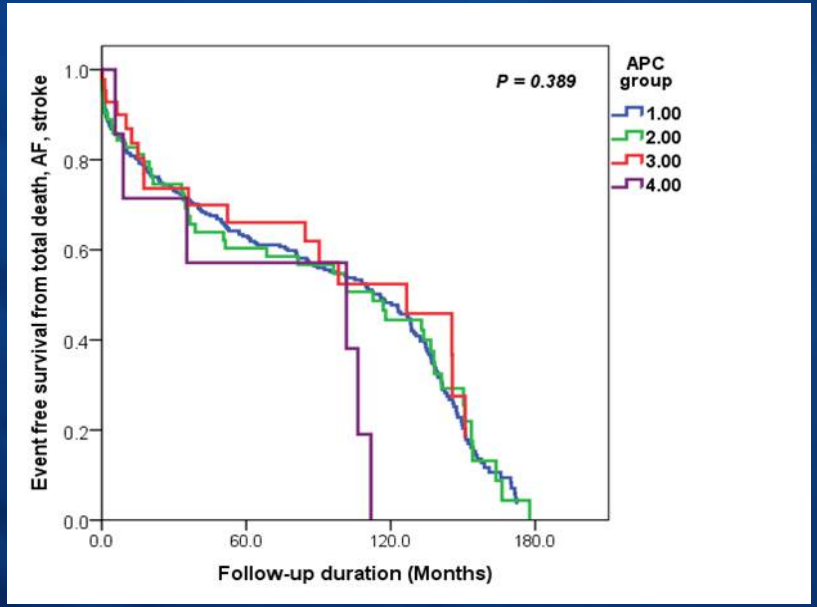
Results 3. Events rates

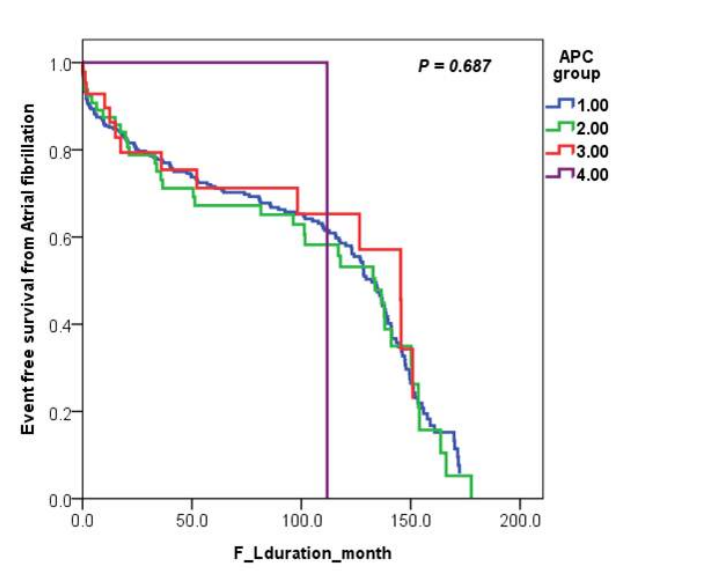
	Gp 1 (n=404)	Gp 2 (n=95)	Gp 3 (n=51)	Gp 4 (n=10)	P value
Any Events (%)					
Stroke	52 (12.9)	14 (14.7)	3 (5.9)	2 (20.0)	0.39
TIA	21 (5.2)	2 (2.1)	2 (3.9)	1 (10.0)	0.53
CMP, non-ischemic	27 (6.7)	5 (5.3)	4 (7.8)	1 (10.0)	0.77
Atrial fibrillation	165 (40.8)	41 (43.2)	15 (29.4)	1 (10.0)	0.09
Death	42 (10.4)	11 (11.6)	6 (11.8)	5 (50.0)	0.02
CV death	21 (5.2)	5 (5.3)	4 (7.8)	3 (30.0)	0.02

Values are expressed as n (%) by independent *t*-test or chi-square test.
TIA, transient ischemic attack; CMP, cardiomyopathy; CV, cardiovascular.

Results 3. Kaplan-Meier estimate







Results 3. Odds ratio of total mortality

Table. Cox analyses for total mortality according to APCs burden

Variable. N (%)	**OR (95% C.I)**	***P* Value**
APCs burden by 24 hours holter monitoring		
Group 1 (100 ~ 5,000 / day) - Control		
Group 2 (5,001 ~10,000 / day)	1.161 (0.574 – 2.347)	0.679
Group 3 (10,001 ~ 20,000 / day)	1.055 (0.396 – 2.813)	0.915
Group 4 (> 20,000/day)	8.651 (2.407 – 31.089)	0.001

Adjusted for age, sex, LA size and APC burden

OR, odds ratio; C.I, confidence interval; APCs, atrial premature complex.

Summary

- During the follow-up of 11.4±3.0 years, 64 deaths (11%) occurred due to any causes
  - 33 deaths (5.8%) occurred due to CVD

- The daily APCs burden was significantly higher in the death than survival group

- Cox regression analysis of the 4 sub-groups revealed that daily APCs burden over 20000 beats was an independent predictor of all-cause mortality (OR: 8.65, 95% CI: 2.40-31.08, P=0.001)

Conclusion

- Extremely frequent daily APCs burden over 20000 beats/ 24 hours is a useful predictor of all-cause mortality including cardiovascular mortality

- For such patients, we propose a close clinical follow up to find and to intervene the risk factors for reduce mortality

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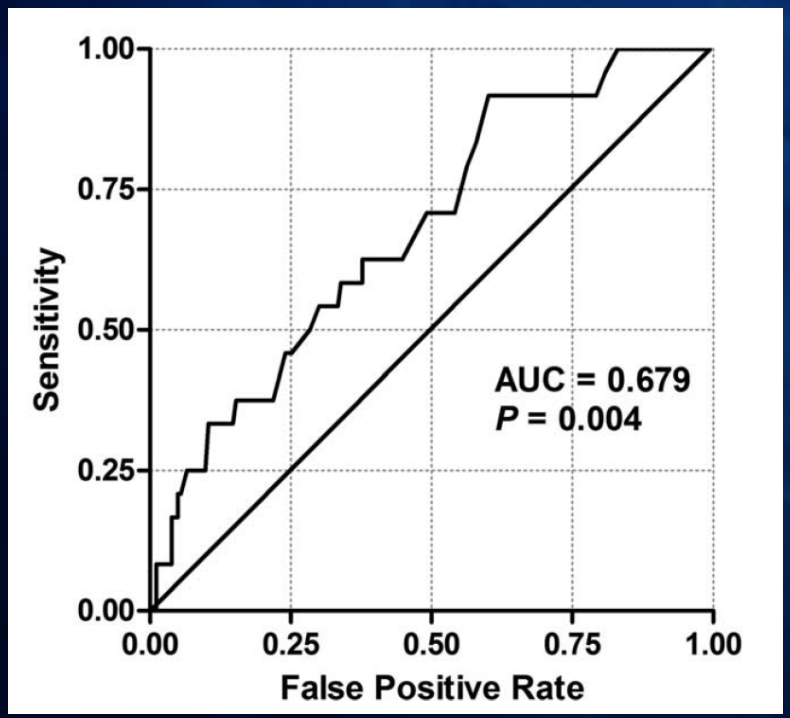
Electrical PR Interval Variation Predicts New Occurrence of Atrial Fibrillation in Patients With Frequent Premature Atrial Contractions

Kwang Jin Chun, MD, Jin Kyung Hwang, MD, Seung-Jung Park, MD, Young Keun On, MD, June Soo Kim, MD, and Kyoung-Min Park, MD



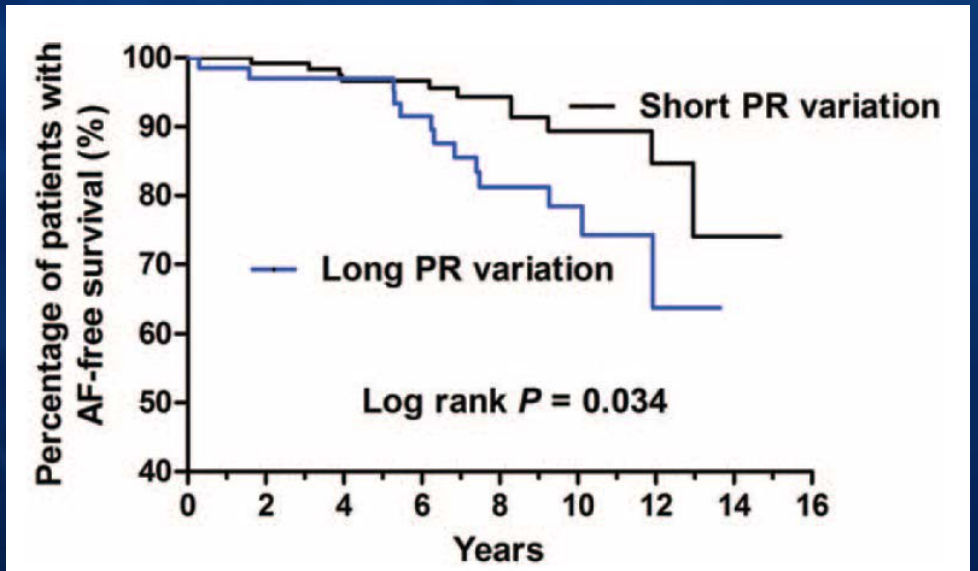


FIGURE 2. Kaplan–Meier estimate of new-onset AF-free survival in patients with frequent PACs. AF = atrial fibrillation, PACs = premature atrial contractions.

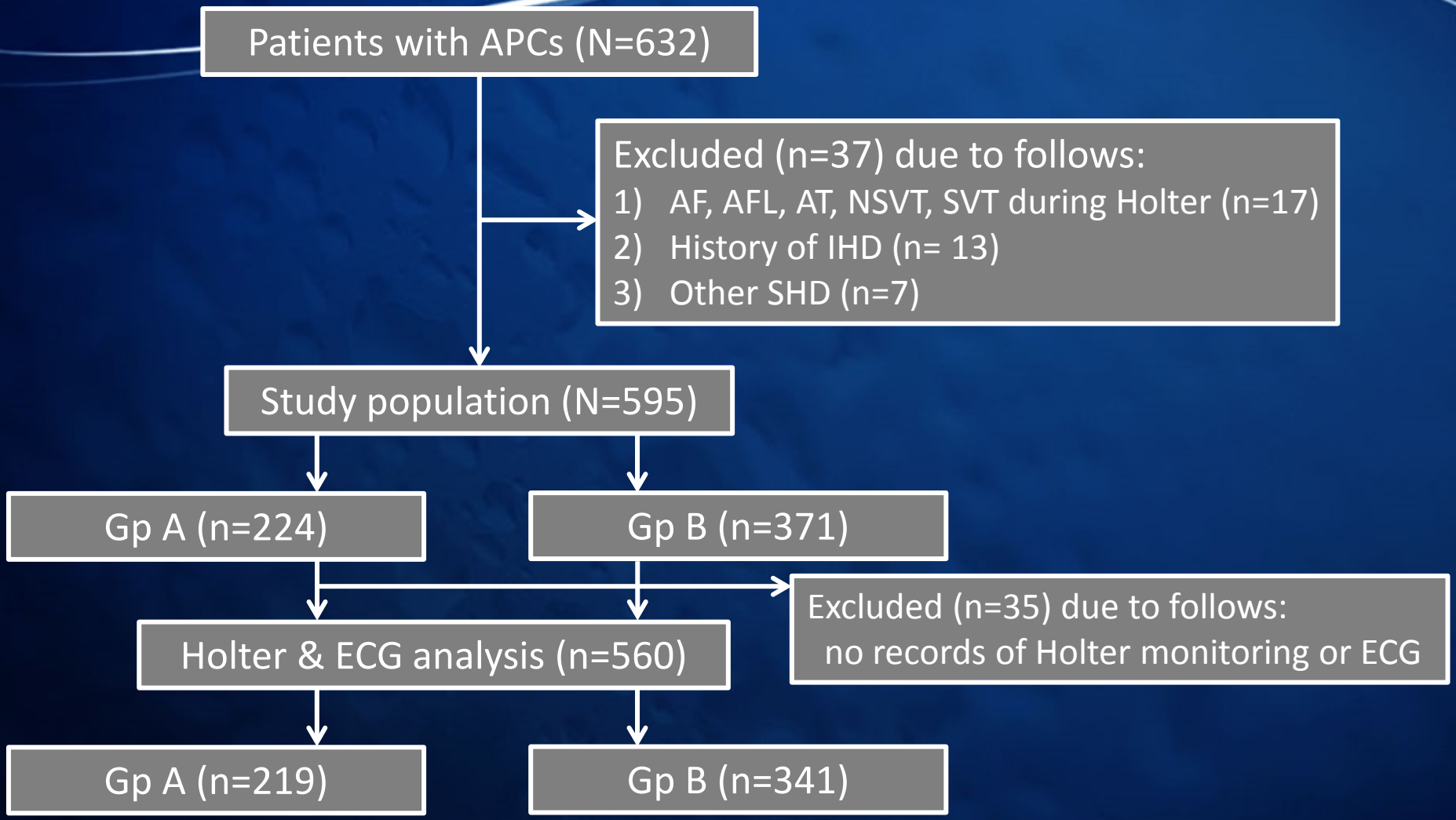
Background

- Premature Atrial Contractions (PACs) are generally considered benign
- However, studies indicate that PACs often precede or forewarn of an AF attack
- Some studies commented about prolonged PR Interval predicts the occurrence of atrial fibrillation

Subjects and Methods

- Study population
  - Jan. 1994 – Dec. 2002, diagnosed with APCs
  - Patients with frequent PACs, more than 100 beats/ day during Holter monitoring, were enrolled in this study
  - The patients who had structural heart disease or atrial fibrillation before the initial Holter monitoring were all excluded
  - Patients were subgrouped into Group (Gp) A (AF) and Gp B (no AF) according to the development of AF during follow-up
  - We analyzed and measured Holter monitoring and ECG signal

Subjects and Methods



Gp A; a patient with atrial fibrillation during follow-up
Gp B; a patient without atrial fibrillation during follow-up

Results 1. Clincial Characteristics

- Mean follow-up: 11.4±3.0 years

	Gp A (n=219)	Gp B (n=341)	p value
Sex, n (%)			<0.001
Male	153 (69.9)	182 (53.4)	
Age (yo)	61.7 ± 12.6	60.2 ± 15.5	0.21
Height (cm)	164.0 ± 9.0	161.5 ± 9.0	0.001
Weight (kg)	64.4 ± 10.4	62.2 ± 10.9	0.01
APC burden (n/24hrs)	4014 ± 4663	4519 ± 5377	0.25
VPC burden (n/24hrs)	1173±4255	1280±4294	0.39
Mean f/u period, years	11.9±3.6	12.1±3.8	0.41
Medical History			
DM	58 (60.3)	65 (35.5)	0.04
HTN	112 (32.6)	174 (35.5)	1.00
Dyslipidemia	3 (23.9)	1 (22.6)	0.30

Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test
APC, atrial premature complexes; DM, diabetes mellitus; HTN, hypertension
VPC, ventricular premature complexes; n, numbers; yo, years old

Results 1. Baseline Characteristics

	Gp A (n=219)	Gp B (n=341)	p value
Symptom, n (%)			
Palpitation	95 (43.4)	118 (34.6)	0.04
Chest pain	63 (28.8)	97 (28.4)	1.00
Dyspnea	56 (25.6)	78 (22.9)	0.48
Dizziness	47 (21.5)	69 (20.2)	0.75
Syncope	29 (13.2)	29 (8.5)	0.08
Fatigue	2 (1.0)	7 (2.1)	0.49

Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test
APC, atrial premature complexes; VPC, ventricular premature complexes; yo, years old

Results 2. Echocardiographic Parameters

	Gp A (n=219)	Gp B (n=341)	p value
EchoCG parameters			
LVEDD (mm)	50.6 ± 6.1	50.6 ± 6.8	0.96
LVESD (mm)	32.2 ± 6.9	31.7 ± 7.4	0.39
LVEF (%)	59.6 ± 10.3	61.0 ± 10.5	0.13
LVPWd (mm)	9.2 ± 2.0	9.0 ± 1.6	0.10
LVSd (mm)	9.3 ± 2.1	9.2 ± 3.6	0.75
LA size (mm)	41.6 ± 7.1	39.8 ± 6.1	0.002

Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test.
LV, left ventricle; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LVEF, LV ejection fraction; LVPWd, LV posterior wall dimension; LVSd, LV septal dimension; LA, left atrium

Results 3. ECG parameters

	Gp A (n=219)	Gp B (n=341)	p value
ECG parameters			
P wave duration	89.3 ± 25.6	86.7 ± 32.8	0.88
PR interval	178 ± 32	165 ± 22	<0.001
P wave amplitude (mV)	1.8 ± 0.5	1.8 ± 0.4	0.95
Δ PR interval (maximun-minimum)	24 ± 37	15 ± 15	0.01

Values are expressed as mean ± SD or n (%) by independent *t*-test or chi-square test.
VPC: ventricular premature complexes, ECG-TTE interval: interval between the day of echocardiogram and the day of transthoracic echocardiography.

Summary

- ECG analysis
  - PR interval and ΔPR interval with serial ECG were significantly higher in patients with AF
- LA size was significantly bigger in patients with AF
- Daily APCs and PVCs burden were not significantly different between two groups

Conclusion

- PR interval and PR interval variability on serial ECG are a good marker to predict the development of atrial fibrillation in patients with frequent PACs

- For such patients, we propose a diagnostic workup with repeated prolonged ECG monitoring to diagnose paroxysmal AF

Limitations

- Retrospective observational study
- Surface ECG analysis could be affected by ECG lead position, cardiac rotation, and respiration
- Rhythm analysis during exercise has limitation
- Frequency of APCs exhibits daily variability, therefore, longer duration of monitoring may preferable

Take Home Message

- “Non-invasive ECG tools” can be used not only to diagnose current arrhythmias, but also to predict various clinical outcomes include atrial fibrillation and all cause mortality
- The ability of our assessment as a predictive tool for atrial fibrillation and all cause mortality also warrants future prospective evaluation
- Moreover, additional long-term prospective studies are needed