Antiarrhythmic Drug Treatment in AF

2015/April/18

춘계심장학회 부산 벡스코

고신의대 차태준

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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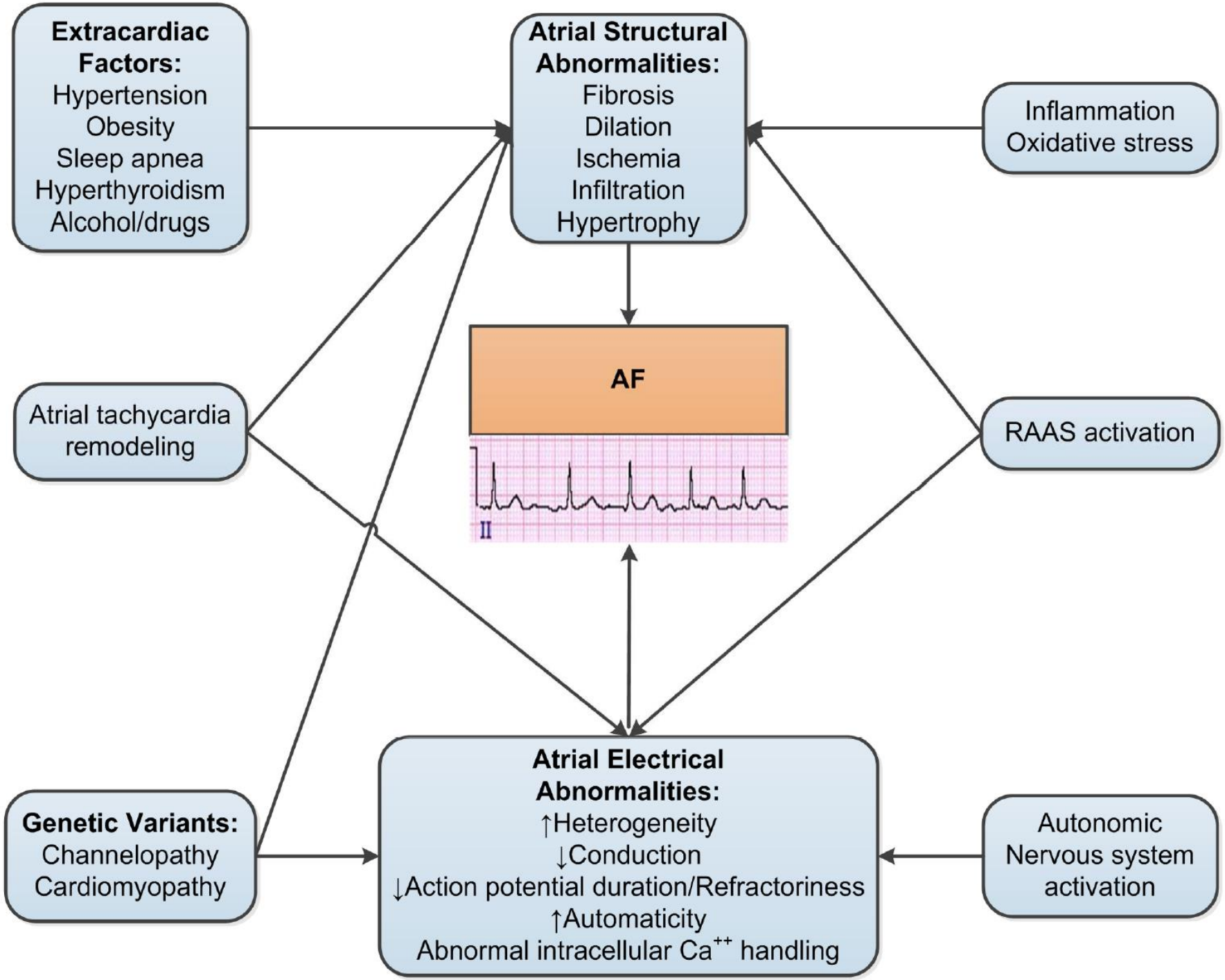
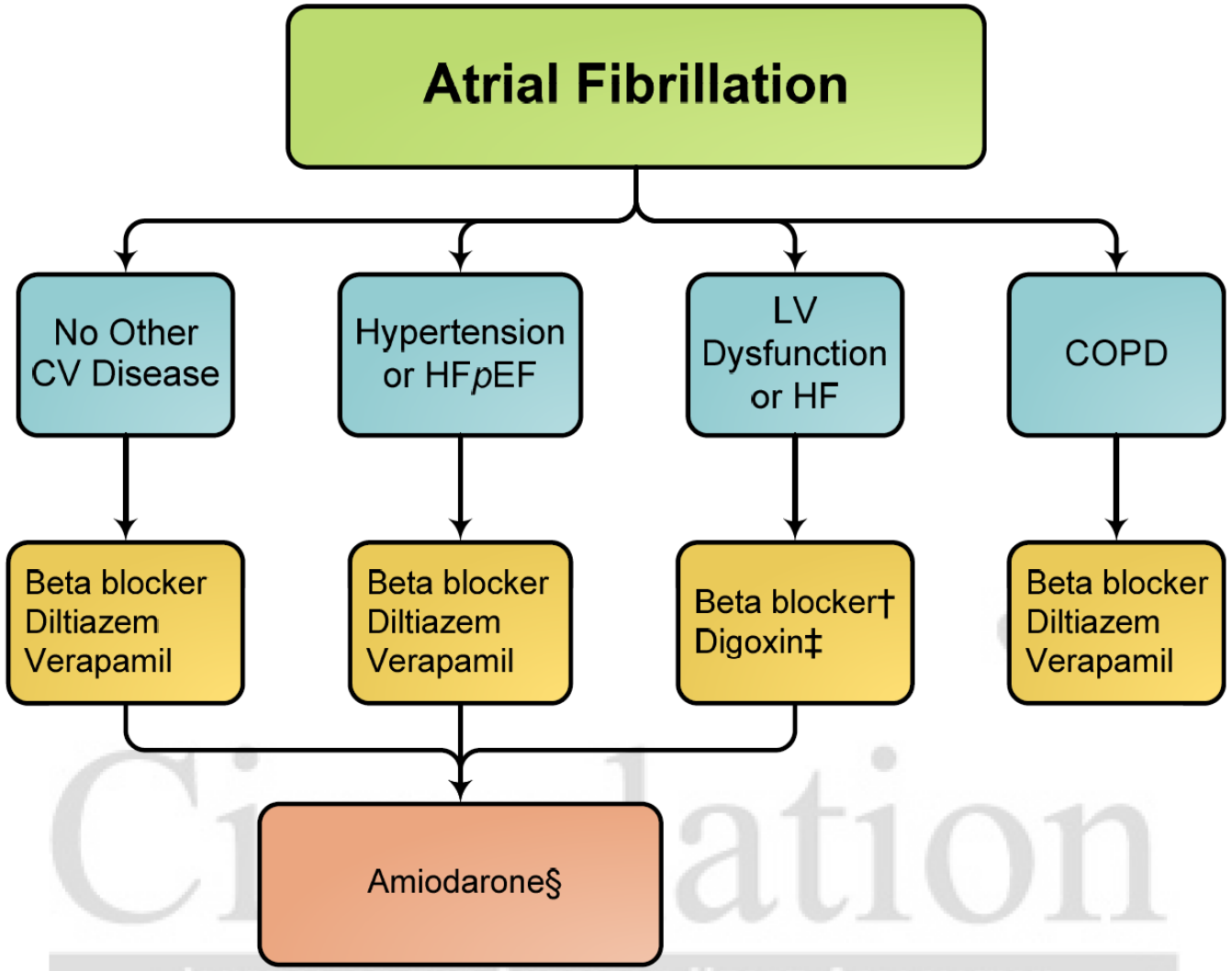

Extracardiac Factors:
Hypertension
Obesity
Sleep apnea
Hyperthyroidism
Alcohol/drugs
Atrial Structural Abnormalities:
Fibrosis
Dilation
Ischemia
Infiltration
Hypertrophy
Inflammation
Oxidative stress
AF
II
Atrial tachycardia remodeling
RAAS activation
Genetic Variants:
Channelopathy
Cardiomyopathy
Atrial Electrical Abnormalities:
↑Heterogeneity
↓Conduction
↓Action potential duration/Refractoriness
↑Automaticity
Abnormal intracellular Ca++ handling
Autonomic Nervous system activation

Rate Control

Recommendations	COR	LOE	References
Control ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF	I	B	(267-269)
IV beta blockers or nondihydropyridine calcium channel blocker recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated	I	B	(270-273)
For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary	I	C	N/A
A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF	IIa	B	(269, 274)
IV amiodarone can be useful for rate control in critically ill patients without pre-excitation	IIa	B	(275-277)
AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological management is inadequate and rhythm control is not achievable	IIa	B	(278-280)
Lenient rate control strategy (resting heart rate <110 bpm) may be reasonable with asymptomatic patients and LV systolic function is preserved	IIb	B	(274)
Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated	IIb	C	N/A
AV nodal ablation should not be performed without prior attempts to achieve rate control with medications	III: Harm	C	N/A
Nondihydropyridine calcium channel antagonists should not be used in decompensated HF	III: Harm	C	N/A
With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone, should not be administered	III: Harm	B	(281)
Dronedarone should not be used to control ventricular rate with permanent AF	III: Harm	B	(282, 283)

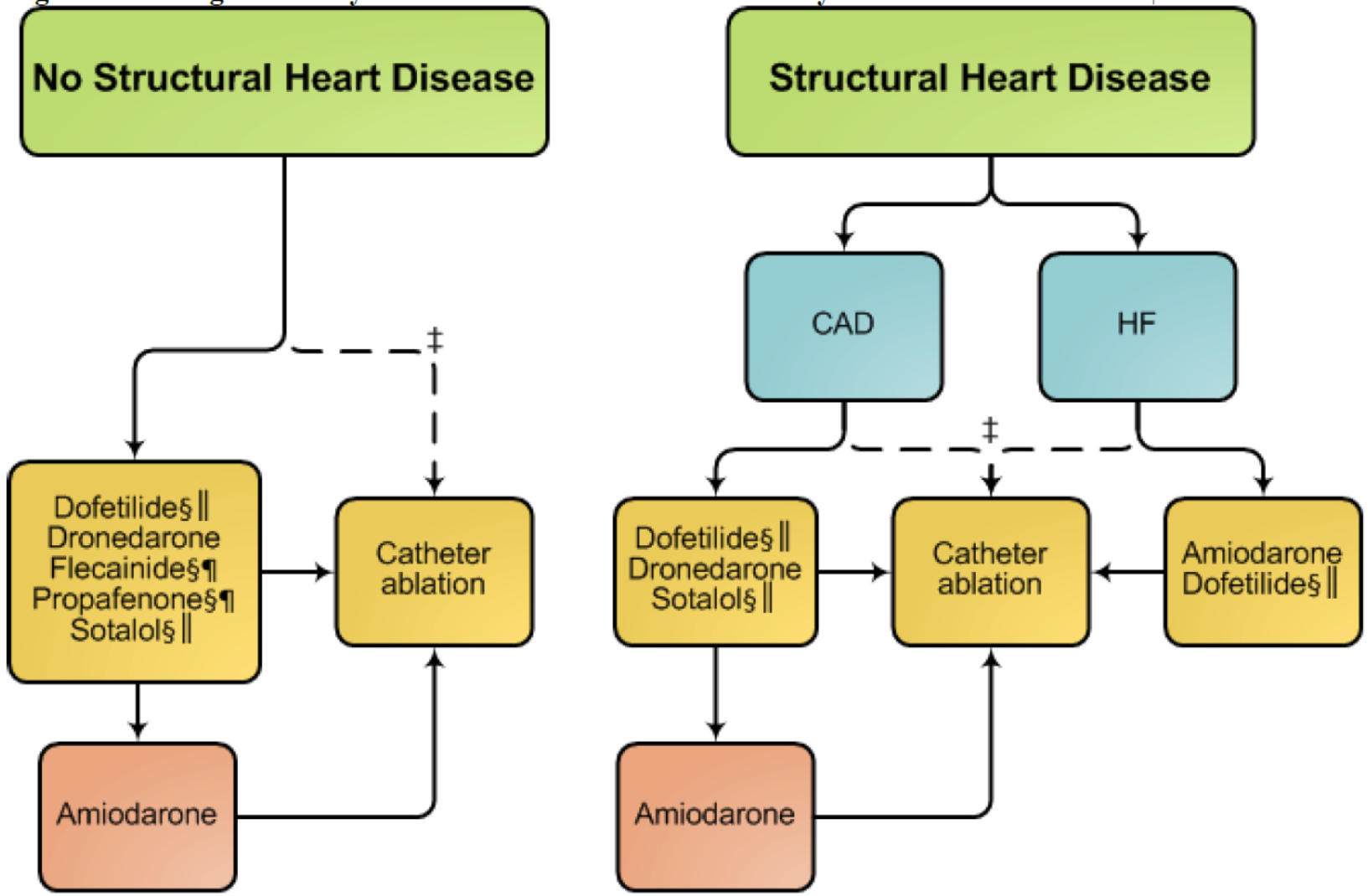
AF indicates atrial fibrillation; AV, atrioventricular; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; and N/A, not applicable.



*Drugs are listed alphabetically.
†Beta blockers should be instituted following stabilization of patients with decompensated HF. The choice of beta blocker (cardio-selective, etc.) depends on the patient's clinical condition.
‡Digoxin is not usually first-line therapy. It may be combined with a beta blocker and/or a nondihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with HF.
§In part because of concern over its side-effect profile, use of amiodarone for chronic control of ventricular rate should be reserved for patients who do not respond to or are intolerant of beta blockers or nondihydropyridine calcium antagonists.

COPD indicates chronic obstructive pulmonary disorder; CV, cardiovascular; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and LV, left ventricular.

Figure 7. Strategies for Rhythm Control in Patients with Paroxysmal* and Persistent AF†



*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation).
†Drugs are listed alphabetically.
‡Depending on patient preference when performed in experienced centers.
§Not recommended with severe LVH (wall thickness >1.5 cm).
‖Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia.
¶Should be combined with AV nodal blocking agents.
AF indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.

Antiarrhythmic Drug Use in Patients <65 Years With Atrial Fibrillation and Without Structural Heart Disease

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Little is known in clinical practice about antiarrhythmic drug (AAD) use in patients with atrial fibrillation (AF) (particularly younger ones) who do not have structural heart disease. Using the MarketScan database, we identified patients <65 years without known coronary artery disease or heart failure who had an AAD prescription claim (class Ic drug, amiodarone, sotalol, or dronedarone) after their first AF encounter. A multinomial logistic regression model was created to assess factors associated with using each available AAD compared with using class Ic drugs before and after dronedarone was marketed in the United States. Additionally, we used the Kaplan-Meier method to determine the rates of change in AAD use and discontinuation during the year after AAD initiation. Of 8,562 patients with AF, 35% received class Ic drugs, 34% amiodarone, 24% sotalol, and 7% dronedarone. The median patient age was 56 (interquartile range 49 to 61), and 34% were women. Both before and after dronedarone was marketed, there was a statistically significant lower likelihood of class Ic drug use versus other AAD use with increasing age, inpatient index AF encounter, and previous or concomitant anticoagulation therapy. During the 1 year after AAD initiation, the AAD change rate was 14% for class Ic drugs, 8% for amiodarone, 17% for sotalol, and 18% for dronedarone ($p < 0.001$); the AAD discontinuation rate was 40% for class Ic drugs, 52% for amiodarone, 40% for sotalol, and 69% for dronedarone ($p < 0.001$). In conclusion, we found extensive use of amiodarone that may be inconsistent with guideline recommendations and unexpectedly high rates of AAD discontinuation. (Am J Cardiol 2015;115:316–322)

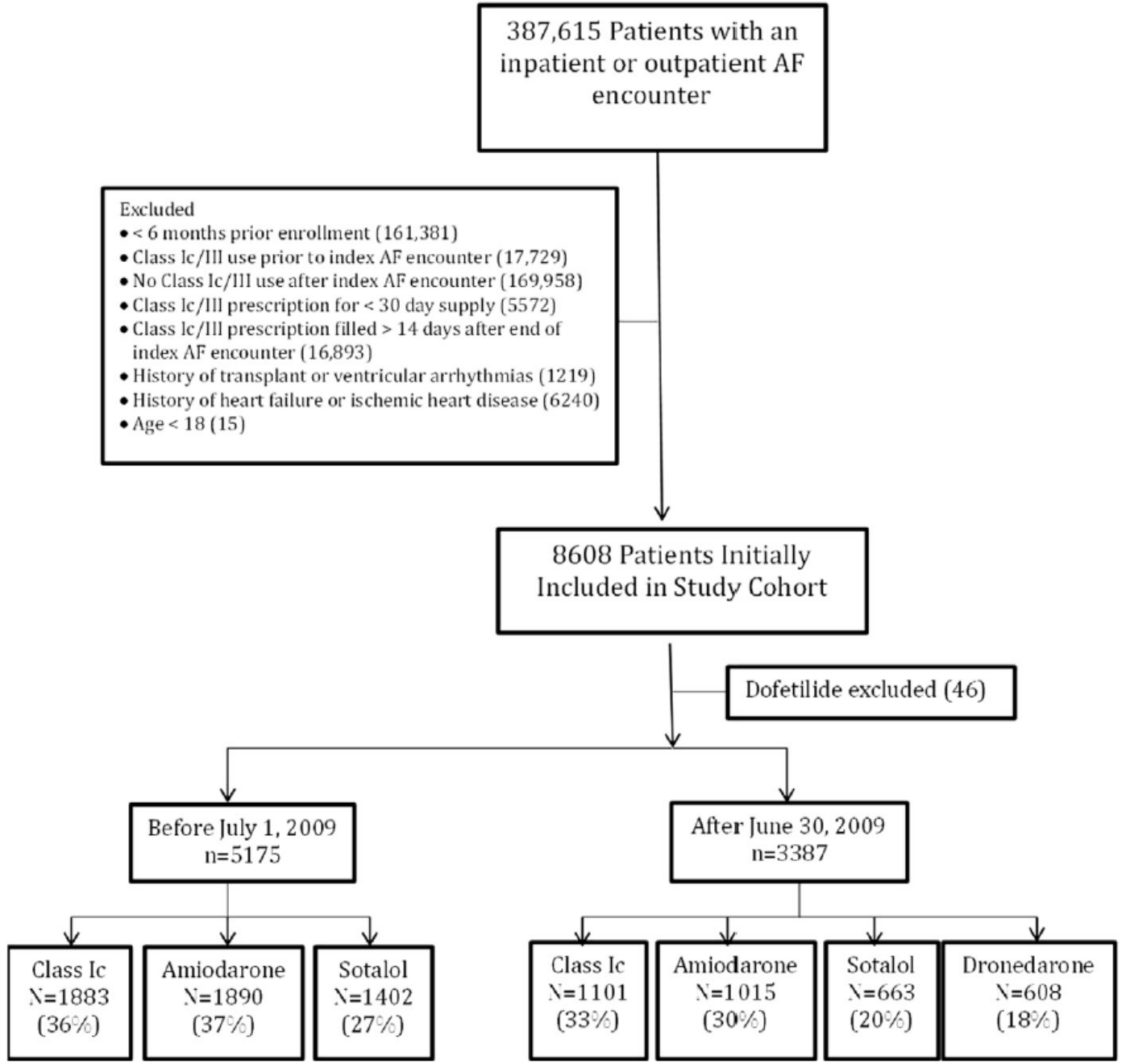
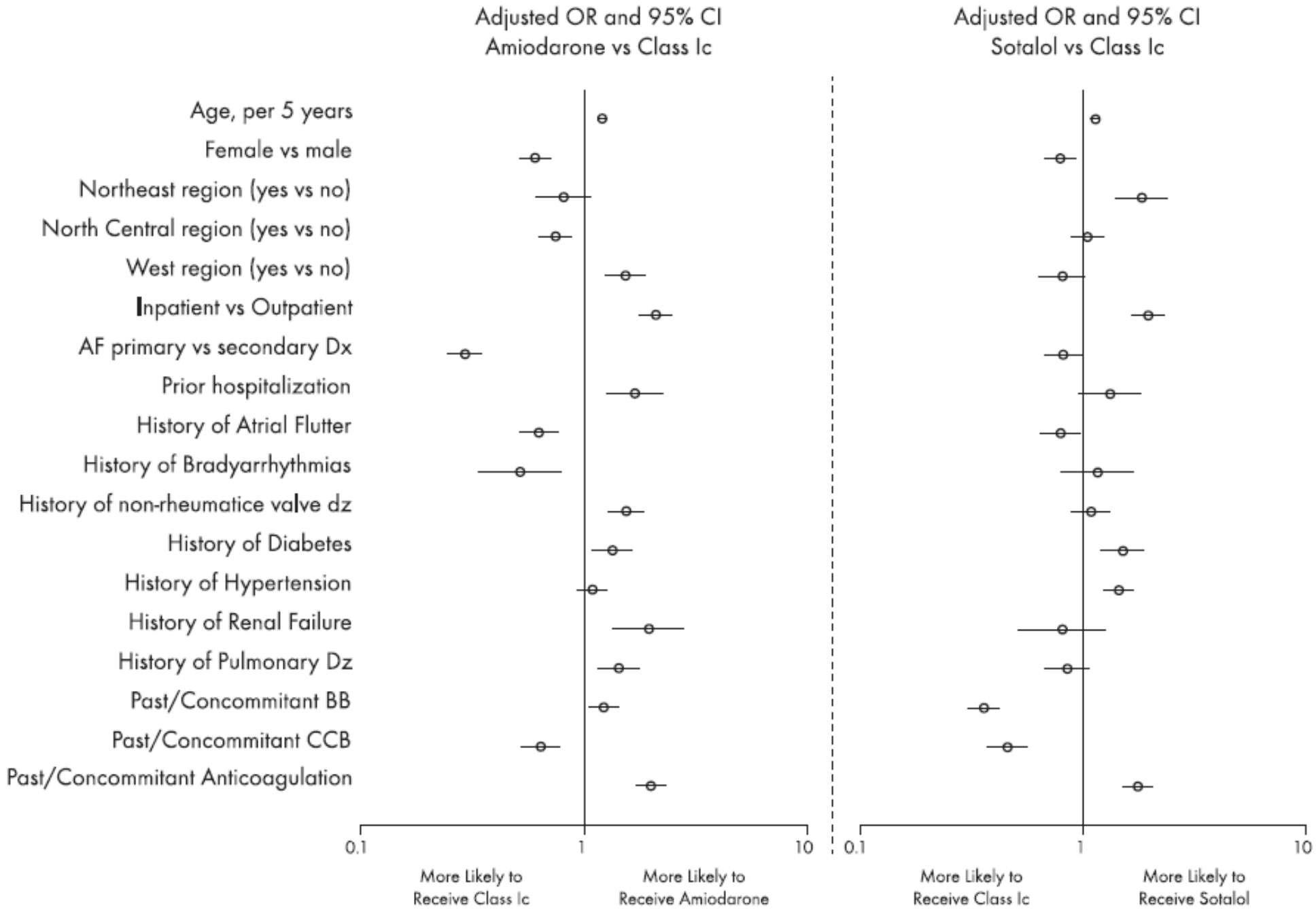


Figure 1. Overall study cohort and subsets of patients by time period.


Adjusted OR and 95% CI
Amiodarone vs Class Ic
Adjusted OR and 95% CI
Sotalol vs Class Ic
Age, per 5 years
Female vs male
Northeast region (yes vs no)
North Central region (yes vs no)
West region (yes vs no)
Inpatient vs Outpatient
AF primary vs secondary Dx
Prior hospitalization
History of Atrial Flutter
History of Bradyarrhythmias
History of non-rheumatice valve dz
History of Diabetes
History of Hypertension
History of Renal Failure
History of Pulmonary Dz
Past/Concommitant BB
Past/Concommitant CCB
Past/Concommitant Anticoagulation
0.1
1
10
More Likely to Receive Class Ic
More Likely to Receive Amiodarone
0.1
1
10
More Likely to Receive Class Ic
More Likely to Receive Sotalol

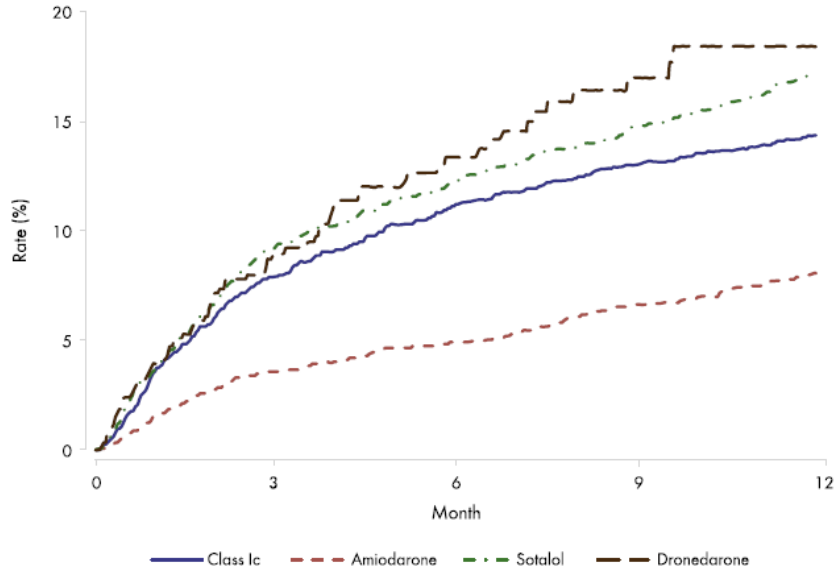


Figure 4. Kaplan-Meier rate of change to different AAD in first year after AAD initiation.

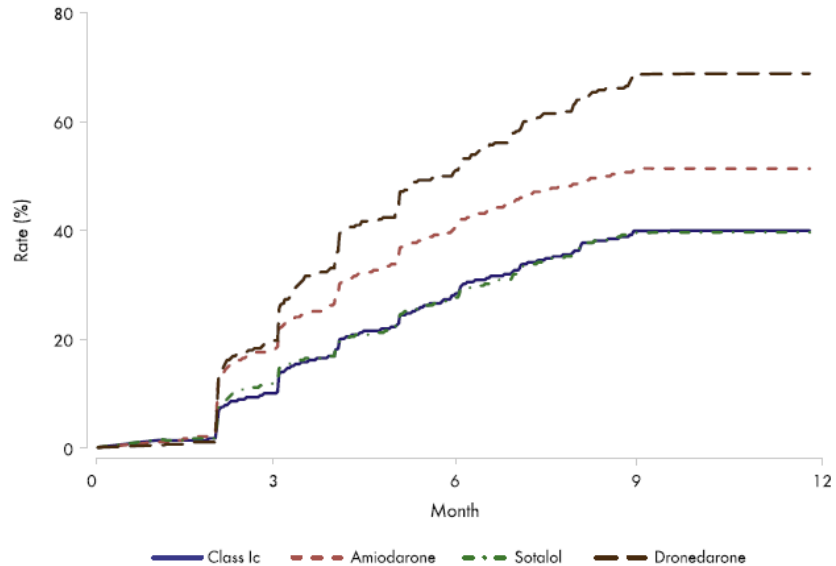


Figure 5. Kaplan-Meier rate of ADD discontinuation by initial antiarrhythmic drug.

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Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events—European Registry in Atrial Fibrillation (PREFER in AF)

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Aims We sought to describe the management of patients with atrial fibrillation (AF) in Europe after the release of the 2010 AF Guidelines of the European Society of Cardiology.

Methods and results The PREFER in AF registry enrolled consecutive patients with AF from January 2012 to January 2013 in 461 centres in seven European countries. Seven thousand two hundred and forty-three evaluable patients were enrolled, aged 71.5 ± 11 years, 60.1% male, CHA_2DS_2VASc score 3.4 ± 1.8 (mean ± standard deviation). Thirty per cent patients had paroxysmal, 24.0% had persistent, 7.2% had long-standing persistent, and 38.8% had permanent AF. Oral anticoagulation was used in the majority of patients: 4799 patients (66.3%) received a vitamin K antagonist (VKA) as mono-therapy, 720 patients a combination of VKA and antiplatelet agents (9.9%), 442 patients (6.1%) a new oral anticoagulant drugs (NOAC). Antiplatelet agents alone were given to 808 patients (11.2%), no antithrombotic therapy to 474 patients (6.5%). Of 7034 evaluable patients, 5530 (78.6%) patients were adequately rate controlled (mean heart rate 60–100 bpm). Half of the patients (50.7%) received rhythm control therapy by electrical cardioversion (18.1%), pharmacological cardioversion (19.5%), antiarrhythmic drugs (amiodarone 24.1%, flecainide or propafenone 13.5%, sotalol 5.5%, dronedarone 4.0%), and catheter ablation (5.0%).

Conclusion The management of AF patients in 2012 has adapted to recent evidence and guideline recommendations. Oral anticoagulant therapy with VKA (majority) or NOACs is given to over 80% of eligible patients, including those at risk for bleeding. Rate is often adequately controlled, and rhythm control therapy is widely used.

Keywords Atrial fibrillation • Management • Registry • Anticoagulation • Stroke • Rhythm control • Catheter ablation • Antiarrhythmic drugs • Rate control • Guidelines • Adherence to guidelines

Table 1 Clinical characteristics of the study population

	Total (*N* = 7243)	France (*N* = 1532)	Germany[a] (*N* = 1771)	Italy (*N* = 1888)	Spain (*N* = 858)	UK (*N* = 1194)
Age (years) (mean)	71.5	72.9	71.9	70.9	70.5	70.7
Height (cm) (mean)	169.2	169.1	171.7	167.3	165.5	171.5
Male (%)	60.1	59.3	63.0	57.0	56.0	64.5
Valvular AF (%)	4.2	5.0	3.3	5.4	5.0	1.9
CHA2DS2VASc score (mean)	3.4	3.3	3.7	3.3	3.3	3.2
Points 1 (%)	10.1	9.2	7.1	11.3	11.7	12.8
Points 2+ (%)	84.1	83.0	89.6	83.4	81.8	80.2
Congestive heart failure (%)[b]	29.0	25.9	36.5	27.6	28.0	24.1
Hypertension (%)[b]	71.8	62.9	81.4	75.4	70.9	62.7
Age ≥ 75 years (%)[b]	44.7	54.8	42.5	42.1	42.5	41.5
Diabetes mellitus (%)[b]	22.7	17.1	31.6	19.8	25.7	18.4
Prior stroke/TIA/thromboembolic event (%)[b]	15.5	13.7	19.1	12.4	12.8	19.0
Vascular disease (%)[b]	22.6	21.5	25.6	22.7	21.6	20.0
Age 65–74 years (%)[b]	32.9	25.4	38.8	34.4	29.4	33.5
Female gender (%)[b]	39.8	40.9	36.8	42.6	43.5	35.7
Heart failure (%)	21.3	18.2	28.4	19.4	24.4	15.4
Ejection fraction (mean)	56.5	59.8	57.0	53.6	58.8	51.1
Hypertension (%)	72.0	63.8	81.9	75.3	72.7	62.1
Diabetes mellitus (%)	22.4	16.8	31.2	19.2	26.4	18.8
Prior stroke (%)	8.4	8.9	10.7	6.5	7.7	8.0
Coronary artery disease (%)	23.4	18.2	29.6	20.6	21.6	26.6
Prior stent (%)	10.2	8.2	14.1	8.9	11.2	8.2
Prior myocardial infarction (%)	10.7	8.0	10.5	11.3	11.2	13.0
Peripheral or aortic artery disease (%)	4.4	5.9	5.0	3.4	4.3	3.4
Chronic kidney disease (%)	12.9	10.1	14.9	12.5	12.7	14.0
Stage 2 (GFR 60–89 mL/min/1.73 m^2) (%)	2.3	1.6	3.2	2.4	2.0	2.0
Stage 3 (GFR 30–59 mL/min/1.73 m^2) (%)	8.3	6.3	9.7	7.0	8.3	10.5
Stage 4 (GFR 15–29 mL/min/1.73 m^2) (%)	1.5	1.6	1.0	2.0	2.1	1.1
Stage 5 (GFR <15 mL/min/1.73 m^2) (%)	0.2	0.1	0.1	0.3	0.2	0.1
Systole/diastole blood pressure (mmHg) at baseline (mean)	132/78	134/78	133/80	129/77	131/76	131/76
Alcohol abuse (%)	2.5	3.6	2.0	1.2	2.6	3.9
Concomitant antiplatelet therapy (%)	22.1	16.9	17.2	27.0	18.7	30.7
Prior bleeding event (%)	7.3	4.1	5.1	7.5	8.7	13.1
Chronic hepatic disease (%)	2.1	1.3	2.2	3.6	1.6	0.7
HASBLED score (mean)	2.0	1.9	2.1	2.1	2.0	2.0
Labile INRs (%)[c]	13.5	15.3	6.6	16.4	18.5	12.1
Elderly (age >65) (%)[c]	75.0	78.4	79.0	73.5	70.7	71.2
Drugs (such as antiplatelet agents, NSAIDs) (%)[c]	27.3	13.8	24.9	32.9	25.0	39.7
Alcohol (alcohol abuse) (%)[c]	2.5	3.4	2.3	1.1	2.9	3.9

NSAID, nonsteroidal anti-inflammatory drug; INR, international normalized ratio; GFR, glomerular filtration rate; HASBLED is an acronym for factors associated with bleeding.[10]
[a]Includes Austria and Switzerland.
[b]Risk factors reported in correlation with CHA_2DS_2VASC score.
[c]Risk factors reported in correlation with HASBLED score.

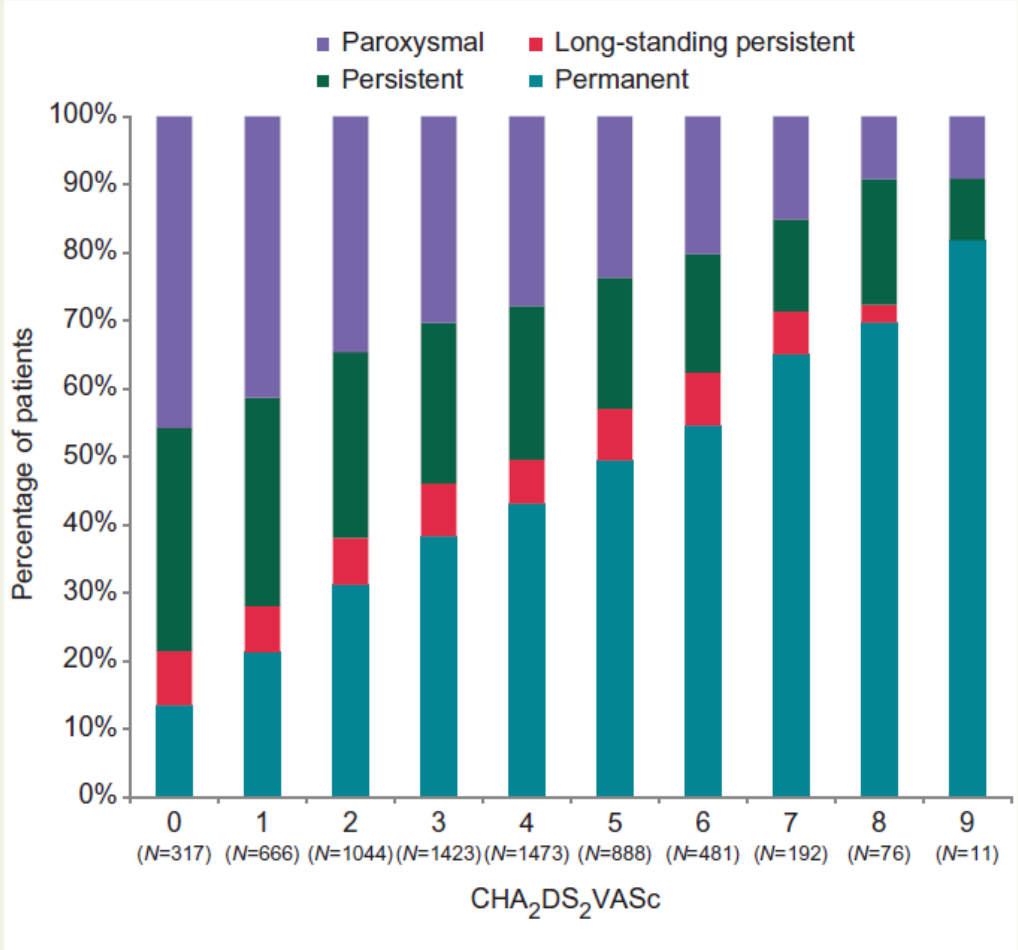

Figure 1 Proportion of patients with a given AF pattern (paroxysmal, persistent, long-standing persistent, or permanent, plotted as percentage, *y* axis) in the study population plotted by the number of concomitant cardiovascular diseases and age as summarized in the CHA_2DS_2VASc score (*x* axis). The proportion of patients with permanent AF increases in each CHA_2DS_2VASc stratum, while the proportion of patients with paroxysmal AF decreases.

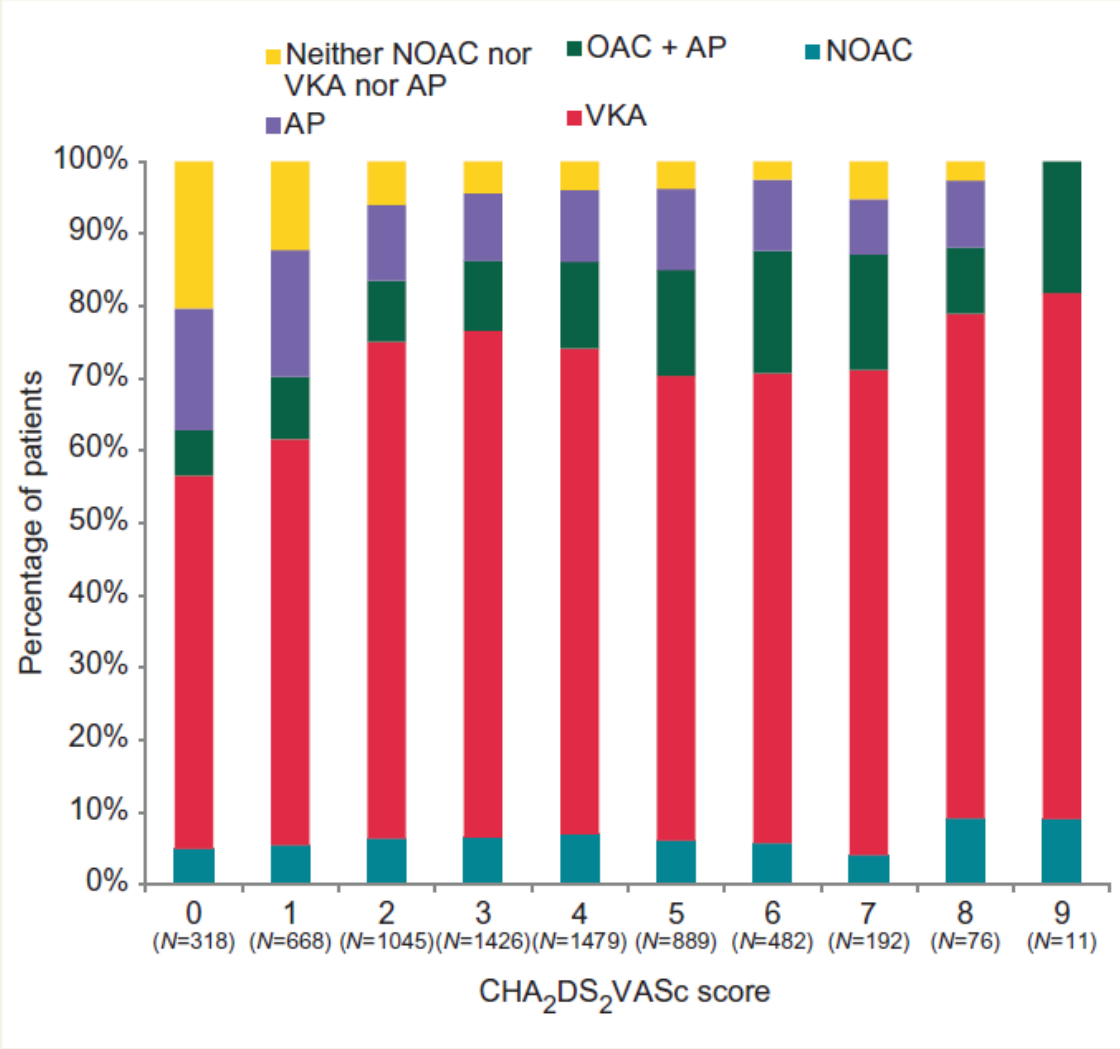

Figure 2 Use of antithrombotic therapy by stroke risk. Most patients with a high stroke risk received adequate anticoagulation, mainly delivered as vitamin K antagonist therapy, antiplatelet agent. VKA vitamin K antagonist, NOAC new oral anticoagulant, OAC oral anticoagulation (either VKA or NOAC).

Table 2 Therapy of the study population

	Total (*n* = 7243)	France (*n* = 1532)	Germany[a] (*n* = 1771)	Italy (*n* = 1888)	Spain (*n* = 858)	UK (*n* = 1194)
Pacemaker/defibrillator, % (*n*)	9.0 (651)	8.4 (126)	9.6 (169)	11.8 (223)	6.5 (56)	6.5 (77)
Antithrombotic therapy (i.e. all OACs), % (*n*)	82.3 (5961)	90.0 (1379)	87.4 (1547)	71.5 (1350)	87.9 (754)	78.0 (931)
Antiplatelets, % (*n*)	22.1 (1599)	16.9 (259)	17.2 (304)	27.0 (510)	18.7 (160)	30.7 (366)
ASA, % (*n*)	19.8 (1436)	14.2 (218)	16.3 (289)	24.4 (460)	16.9 (145)	27.1 (324)
Clopidogrel, % (*n*)	4.1 (293)	3.5 (54)	2.4 (43)	4.6 (87)	4.4 (38)	6.0 (71)
Prasugrel, % (*n*)	0.3 (23)	0.1 (1)	0.3 (6)	0.5 (9)	0.7 (6)	0.1 (1)
Ticagrelor, % (*n*)	0.1 (5)	0.0 (0)	0.1 (1)	0.1 (2)	0.0 (0)	0.2 (2)
Vitamin K antagonists, % (*n*)	78.0 (5649)	86.0 (1318)	79.1 (1400)	71.4 (1348)	80.0 (686)	75.1 (897)
Warfarin, % (*n*)	34.1 (2470)	16.1 (246)	2.8 (50)	62.0 (1171)	12.7 (109)	74.9 (894)
Phenprocoumon, % (*n*)	18.4 (1330)	1.0 (16)	74.1 (1313)	0.0 (0)	0.0 (0)	0.1 (1)
Fluindione, % (*n*)	13.1 (948)	61.8 (947)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)
Acenocoumarol, % (*n*)	12.5 (907)	7.2 (110)	2.0 (35)	9.6 (181)	67.3 (577)	0.3 (4)
New oral anticoagulants, % (*n*)	6.1 (442)	6.0 (92)	11.6 (205)	0.3 (5)	11.2 (96)	3.7 (44)
Dabigatran, % (*n*)	4.0 (291)	5.0 (76)	5.5 (97)	0.2 (3)	8.9 (76)	3.3 (39)
Rivaroxaban, % (*n*)	1.9 (140)	1.0 (16)	5.8 (102)	0.0 (0)	2.3 (20)	0.2 (2)
Apixaban, % (*n*)	0.1 (8)	0.0 (0)	0.2 (4)	0.1 (1)	0.1 (1)	0.2 (2)
Antiplatelets as mono-therapy, % (*n*)	11.2 (808)	5.9 (91)	7.6 (135)	18.1 (342)	6.4 (55)	15.5 (185)
Vitamin K antagonists as mono-therapy, % (*n*)	66.3 (4799)	74.0 (1133)	68.1 (1206)	62.4 (1178)	66.4 (570)	59.6 (712)
New oral anticoagulants as mono-therapy or in combination, % (*n*)	6.1 (442)	6.0 (92)	11.6 (205)	0.3 (5)	11.2 (96)	3.7 (44)
No antithrombotic therapy, % (*n*)	6.5 (474)	4.1 (62)	5.0 (89)	10.4 (196)	5.7 (49)	6.5 (78)
Combination therapy of antiplatelet agents and oral anticoagulation, % (*n*)	10.9 (791)	11.0 (168)	9.5 (169)	8.9 (168)	12.2 (105)	15.2 (181)
Mean heart rate (bpm) at enrolment mean (25–75% quartiles)[b]	79.1 (67.0–88.0)	74.5 (64.0–83.0)	80.3 (69.0–90.0)	80.8 (68.0–90.0)	78.3 (68.0–88.0)	81.4 (67.0–93.0)
Sinus rhythm, % (*n*)	31.4 (2254)	36.3 (546)	25.1 (442)	38.0 (710)	34.2 (293)	22.3 (263)
Patients with adequate heart rate control (HR 60–100), % (*n*)	78.6 (5530)	79.4 (1186)	81.4 (1401)	78.7 (1452)	79.5 (673)	72.5 (818)
Patients with acceptable heart rate control (HR 50–59 or 101–110), % (*n*)	14.3 (1005)	14.9 (223)	12.2 (210)	13.8 (255)	15.5 (131)	16.5 (186)
Patients without adequate heart rate control (HR<50 or >110), % (*n*)	7.1 (499)	5.6 (84)	6.4 (110)	7.5 (138)	5.1 (43)	11.0 (124)
Rhythm control therapy, % (*n*)	59.8 (4332)	72.3 (1107)	54.6 (966)	66.0 (1246)	50.2 (431)	48.7 (582)
Amiodarone, % (*n*)	24.1 (1746)	40 (613)	14.1 (250)	29.8 (562)	21.5 (184)	11.5 (137)
Dronedarone, % (*n*)	4.0 (291)	2.7 (41)	7.5 (132)	2.1 (40)	6.3 (54)	2.0 (24)
Flecainide, % (*n*)	10.6 (764)	17.5 (268)	6.2 (110)	12.0 (226)	12.0 (103)	4.8 (57)
Propafenone, % (*n*)	2.9 (211)	2.0 (30)	1.3 (23)	7.3 (138)	1.9 (16)	0.3 (4)
d,l-Sotalol, % (*n*)	5.5 (396)	8.5 (130)	4.7 (83)	4.6 (86)	1.8 (15)	6.9 (82)
Quinidine, % (*n*)	0.2 (13)	0.5 (8)	0.1 (1)	0.2 (4)	0.0 (0)	0.0 (0)
Catheter ablation done in the past 12 months, % (*n*)	5.0 (358)	4.7 (71)	5.8 (102)	4.4 (83)	3.7 (32)	5.9 (70)
Electrical cardioversion done in the past 12 months, % (*n*)	18.1 (1306)	14.4 (216)	19.1 (337)	21.0 (394)	14.5 (124)	19.7 (235)
Pharmacological cardioversion done in the past 12 months, % (*n*)	19.5 (1403)	26.1 (391)	12.8 (226)	27.3 (512)	17.7 (152)	10.2 (122)

HR, heart rate.
[a]Includes Austria and Switzerland.
[b]Ventricular rate during AF.

Table 3 Adequacy of rate control therapy by symptom status

	EHRA I[a] (*N* = 534)	EHRA II[a] (*N* = 2594)	EHRA III[a] (*N* = 2335)	EHRA IV[a] (*N* = 1516)
Patients with adequate heart rate control (HR 60–100)	431 (80.7)	2099 (80.9)	1834 (78.5)	1129 (74.5)
Patients with acceptable heart rate control (HR 50–59 or 101–110)	75 (14.0)	344 (13.3)	334 (14.3)	242 (16.0)
Patients without adequate heart rate control (HR<50 or >110)	28 (5.2)	151 (5.8)	167 (7.2)	145 (9.6)
Total	534 (99.9)	2594 (100.0)	2335 (100.0)	1516 (100.1)

HR, heart rate.

[a]The EHRA score was determined as the maximum of the six individual symptoms scores (palpitations, fatigue, dizziness, dyspnea, chest pain, anxiety). Each of these symptoms was scored by the enrolling physician as follows: never, occasional, intermediate, frequent. The EHRA score was then defined as follows: I, maximum score of 'never'; II, maximum score of 'occasional'; III, maximum score of 'intermediate'; IV, maximum score of 'frequent'.[9]

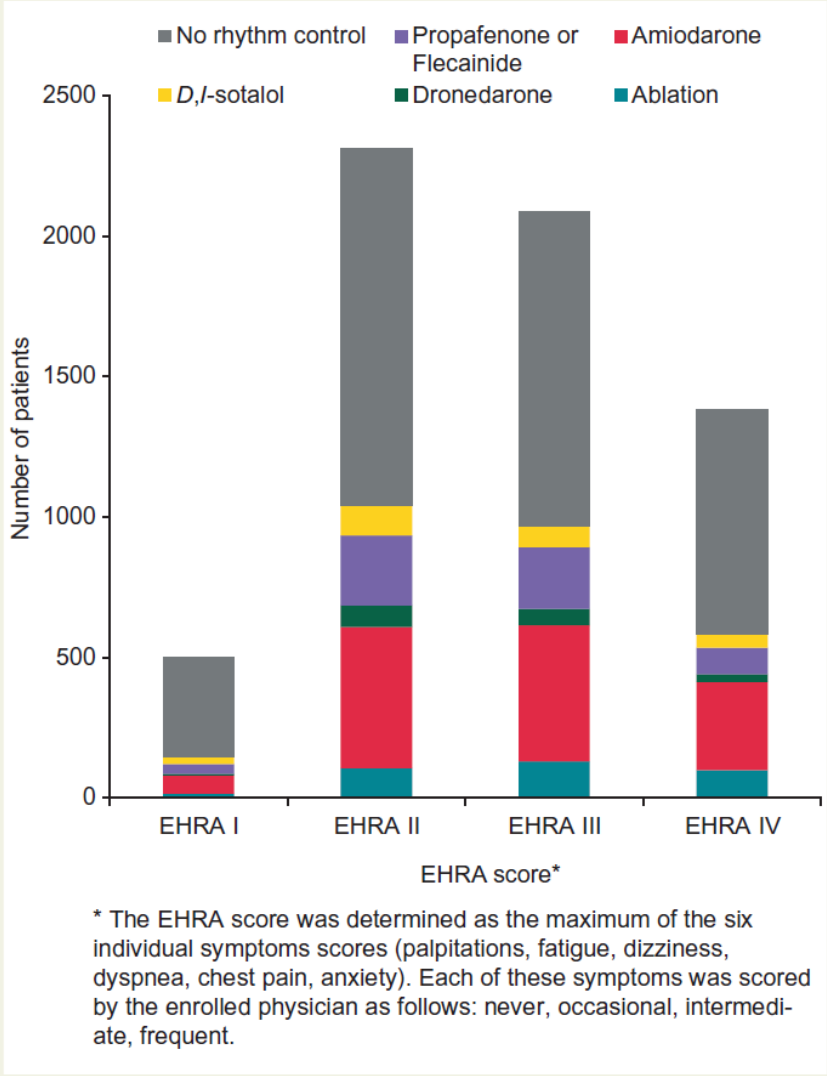

Figure 4 Use of rhythm control therapy options by patient symptoms. Following clinical reasoning and the recommendations in the ESC guidelines, rhythm control therapy was rarely used in asymptomatic patients. The EHRA score is calculated as the maximum of the six symptoms score (palpitations, fatigue, dizziness, dyspnea, chest pain, anxiety) as explained in the legend to *Table 3*.

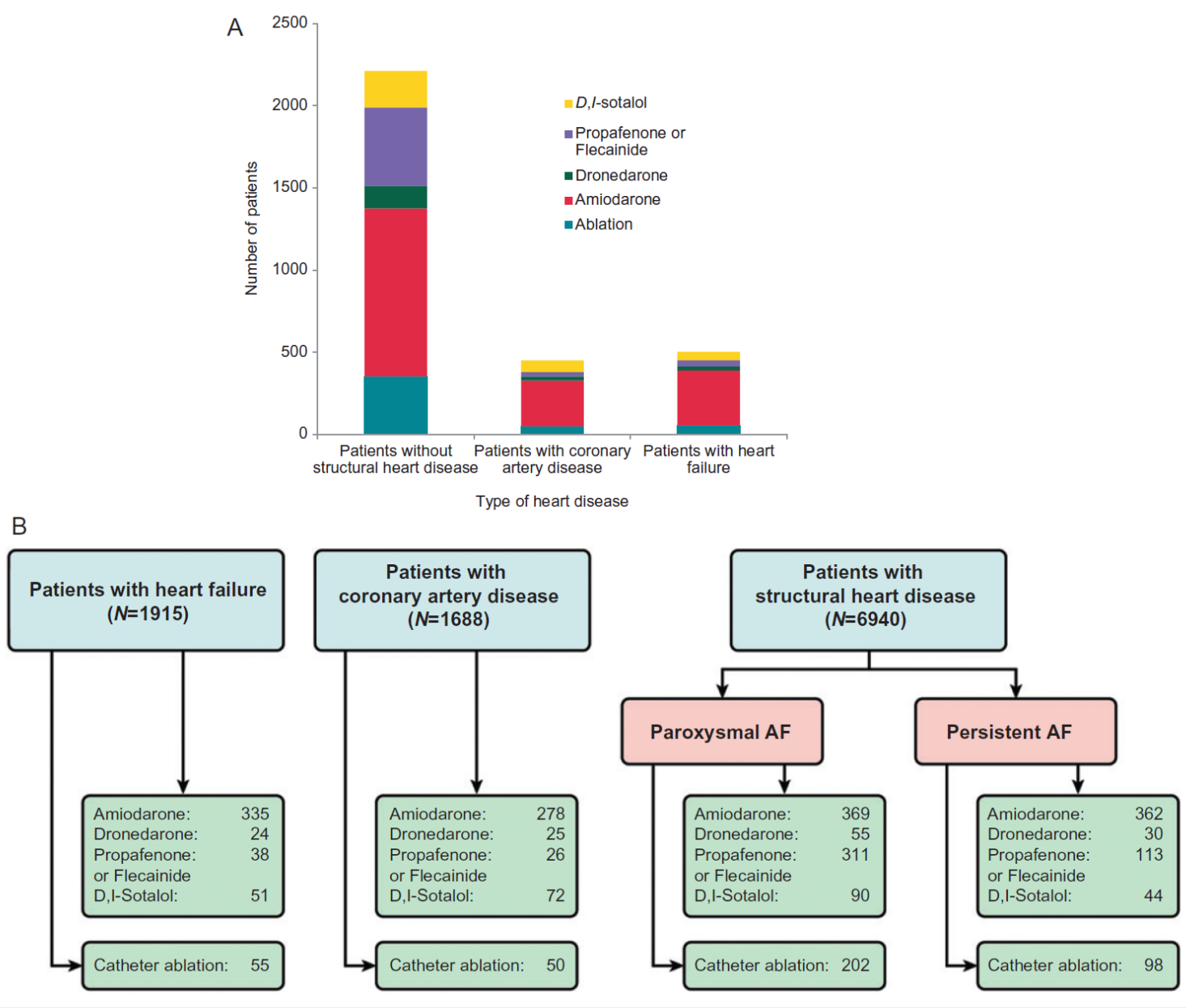

Figure 5 Type of rhythm control therapy by type of heart disease. (*A*) Stacked column graph depicting the use of the different antiarrhythmic drugs and catheter ablation in patients with different types of heart disease (coronary artery disease, heart failure, no structural heart disease). (*B*) Illustration of the use of rhythm control therapies in patients with different types of heart disease in a flow chart illustrating the recommendations of the ESC 2010 guidelines for AF. All numbers reflect the actual patient number.

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Prognosis and treatment of atrial fibrillation patients by European cardiologists: One Year Follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry)

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Background The EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot) provides systematic collection of contemporary data regarding the management and treatment of 3119 subjects with AF from 9 member European Society of Cardiology (ESC) countries. In this analysis, we report the development of symptoms, use of antithrombotic therapy and rate vs. rhythm strategies, as well as determinants of mortality and/or stroke/transient ischaemic attack (TIA)/peripheral embolism during 1-year follow-up in this contemporary European registry of AF patients.

Methods The registry population comprised consecutive in- and out-patients with AF presenting to cardiologists in participating ESC countries. Consecutive patients with AF documented by ECG were enrolled. Follow-up was performed by the local investigator, initially at 1 year, as part of a long-term cohort study.

Results At the follow-up, patients were frequently asymptomatic (76.8%), but symptoms are nevertheless common among paroxysmal and persistent AF patients, especially palpitations, fatigue, and shortness of breath. Oral anticoagulant (OAC) use remains high, ~78% overall at follow-up, and of those on vitamin K antagonist (VKA), 84% remained on VKA during the follow-up, while of those on non-VKA oral anticoagulant (NOAC) at baseline, 86% remained on NOAC, and 11.8% had changed to a VKA and 1.1% to antiplatelet therapy. Digitalis was commonly used in paroxysmal AF patients. Of rhythm control interventions, electrical cardioversion was performed in 9.7%, pharmacological cardioversion in 5.1%, and catheter ablation in 4.4%. Despite good adherence to anticoagulation, 1-year mortality was high (5.7%), with most deaths were cardiovascular (70%). Hospital readmissions were common, especially for atrial tachyarrhythmias and heart failure. On multivariate analysis, independent baseline predictors for mortality and/or stroke/TIA/peripheral embolism minor bleeding. Independent predictors of mortality were age, chronic kidney disease, AF as primary presentation, prior TIA, chronic obstructive pulmonary disease, malignancy, minor bleeding, and diuretic use. Statin use was predictive of lower mortality.

Conclusion In this 1-year follow-up analysis of the EORP-AF pilot general registry, we provide data on the first contemporary registry focused on management practices among European cardiologists, conducted since the publication of the new ESC guidelines. Overall OAC use remains high, although persistence with therapy may be problematic. Nonetheless, continued OAC use was more common than in prior reports. Despite the high prescription of OAC, 1-year mortality and morbidity remain high in AF patients, particularly from heart failure and hospitalizations.

Keywords Atrial fibrillation • Stroke • Mortality • Prognosis • Registry

Table 1 Patient demography in relation to clinical subtype of atrial fibrillation

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
Age (years) (mean ± SD)	68.7 ± 11.6 ($n = 2589$)	68.4 ± 12.4 ($n = 774$)	66.7 ± 11.4 ($n = 693$)	67.9 ± 11.0 ($n = 550$)	70.9 ± 10.8 ($n = 121$)	73.0 ± 10.2 ($n = 451$)	<0.0001**
Age (years) [Median (IQR)]	69.0 (62.0–77.0) ($n = 2589$)	70.0 (61.0–77.0) ($n = 774$)	67.0 (60.0–75.0) ($n = 693$)	69.0 (61.0–75.0) ($n = 550$)	69.0 (63.0–79.0) ($n = 121$)	74.0 (66.0–81.0) ($n = 451$)	
Age (years, %)							
≤65	36.5 (945/2589)	36.3 (281/774)	44.2 (306/693)	39.5 (217/550)	29.8 (36/121)	23.3 (105/451)	<0.0001*
>65	63.5 (1644/2589)	63.7 (493/774)	55.8 (387/693)	60.5 (333/550)	70.2 (85/121)	76.7 (346/451)	
Gender (%)							
Male	60.6 (1568/2589)	64.2 (497/774)	58.4 (405/693)	60.4 (332/550)	61.2 (74/121)	57.6 (260/451)	0.1232*
Female	39.4 (1021/2589)	35.8 (277/774)	41.6 (288/693)	39.6 (218/550)	38.8 (47/121)	42.4 (191/451)	
CHA_2DS_2-VASc (%)							
Low risk	8.3 (215/2589)	7.5 (58/774)	13.9 (96/693)	7.6 (42/550)	3.3 (4/121)	3.3 (15/451)	<0.0001*
Moderate risk	10.5 (273/2589)	11.9 (92/774)	13.1 (91/693)	11.1 (61/550)	8.3 (10/121)	4.2 (19/451)	
High risk	81.2 (2101/2589)	80.6 (624/774)	73.0 (506/693)	81.3 (447/550)	88.4 (107/121)	92.5 (417/451)	
HAS-BLED Score class (%)							
0–2	86.0 (2227/2589)	85.7 (663/774)	89.3 (619/693)	86.9 (478/550)	79.3 (96/121)	82.3 (371/451)	0.0024*
3 or more	14.0 (362/2589)	14.3 (111/774)	10.7 (74/693)	13.1 (72/550)	20.7 (25/121)	17.7 (80/451)	
Follow-up duration (days) (mean ± SD)	366.4 ± 31.8 ($n = 2421$)	367.6 ± 30.2 ($n = 705$)	365.9 ± 32.6 ($n = 663$)	366.6 ± 29.3 ($n = 522$)	362.6 ± 22.6 ($n = 114$)	365.8 ± 37.6 ($n = 417$)	<0.0001**
Follow-up duration (days) [median (IQR)]	366.0 (359.0–378.0) ($n = 2421$)	367.0 (359.0–379.0) ($n = 705$)	365.0 (358.0–377.0) ($n = 663$)	367.0 (361.0–379.0) ($n = 522$)	363.0 (357.0–367.0) ($n = 114$)	369.0 (362.0–382.0) ($n = 417$)	
Current symptoms at 1-year follow-up (%)	23.2 (562/2423)	17.6 (124/705)	24.8 (165/665)	27.8 (145/522)	14.9 (17/114)	26.6 (111/417)	<0.0001*
Palpitations (%)	65.3 (367/562)	62.1 (77/124)	77.0 (127/165)	65.5 (95/145)	52.9 (9/17)	53.2 (59/111)	0.0008*
Dizziness (%)	18.7 (105/562)	26.6 (33/124)	18.2 (30/165)	14.5 (21/145)	23.5 (4/17)	15.3 (17/111)	0.0940*
General non-wellbeing (%)	30.4 (171/562)	33.9 (42/124)	31.5 (52/165)	31.0 (45/145)	47.1 (8/17)	21.6 (24/111)	0.1307*
Fatigue (%)	50.0 (281/562)	58.1 (72/124)	41.8 (69/165)	47.6 (69/145)	64.7 (11/17)	54.1 (60/111)	0.0375*
Shortness of breath (%)	43.1 (242/562)	39.5 (49/124)	38.2 (63/165)	46.2 (67/145)	70.6 (12/17)	45.9 (51/111)	0.0763*
Chest pain (%)	11.7 (66/562)	10.5 (13/124)	13.9 (23/165)	10.3 (15/145)	29.4 (5/17)	9.0 (10/111)	0.1281*
Fear/anxiety (%)	12.1 (68/562)	12.1 (15/124)	14.5 (24/165)	12.4 (18/145)	17.6 (3/17)	7.2 (8/111)	0.4154*
Other (%)	4.8 (27/562)	3.2 (4/124)	6.1 (10/165)	4.1 (6/145)	5.9 (1/17)	5.4 (6/111)	0.8237*

This table is focused on 2589 patients where the demographics are being presented on this subpopulation—of the total 3119 patients at baseline, we had removed 10 dead patients at discharge and removed 467 patients lost to follow-up; removed 53 patients with type of AF unknown. The definitions were investigator-categorized and were based on the ESC guidelines. Long-standing persistent is where there is a decision not to perform catheter ablation anymore and was intended to replace the cohort 'permanent' in ablation-focused reports.

*P-values for among-group comparisons are from Pearson's χ^2 test.

**P-values for among-group comparisons are from the Kruskal–Wallis test.

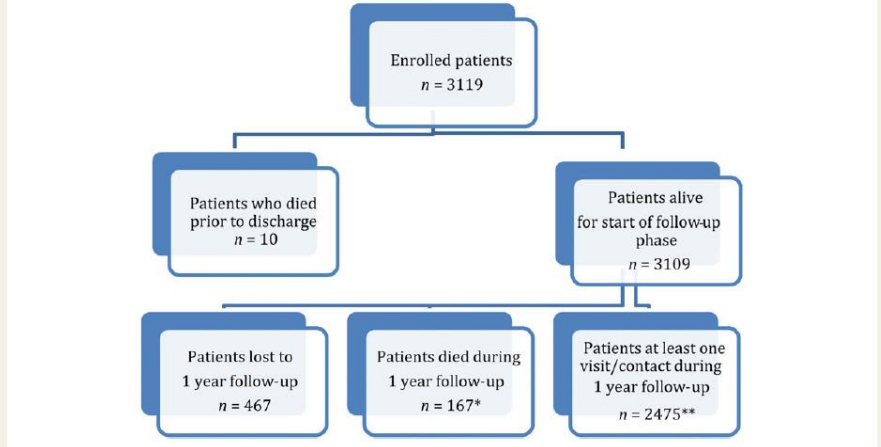

Figure 1 Patient flow as part of the EORP-AF pilot general registry. *1 Patient with type of atrial fibrillation unknown. **52 Patients with type of atrial fibrillation unknown.

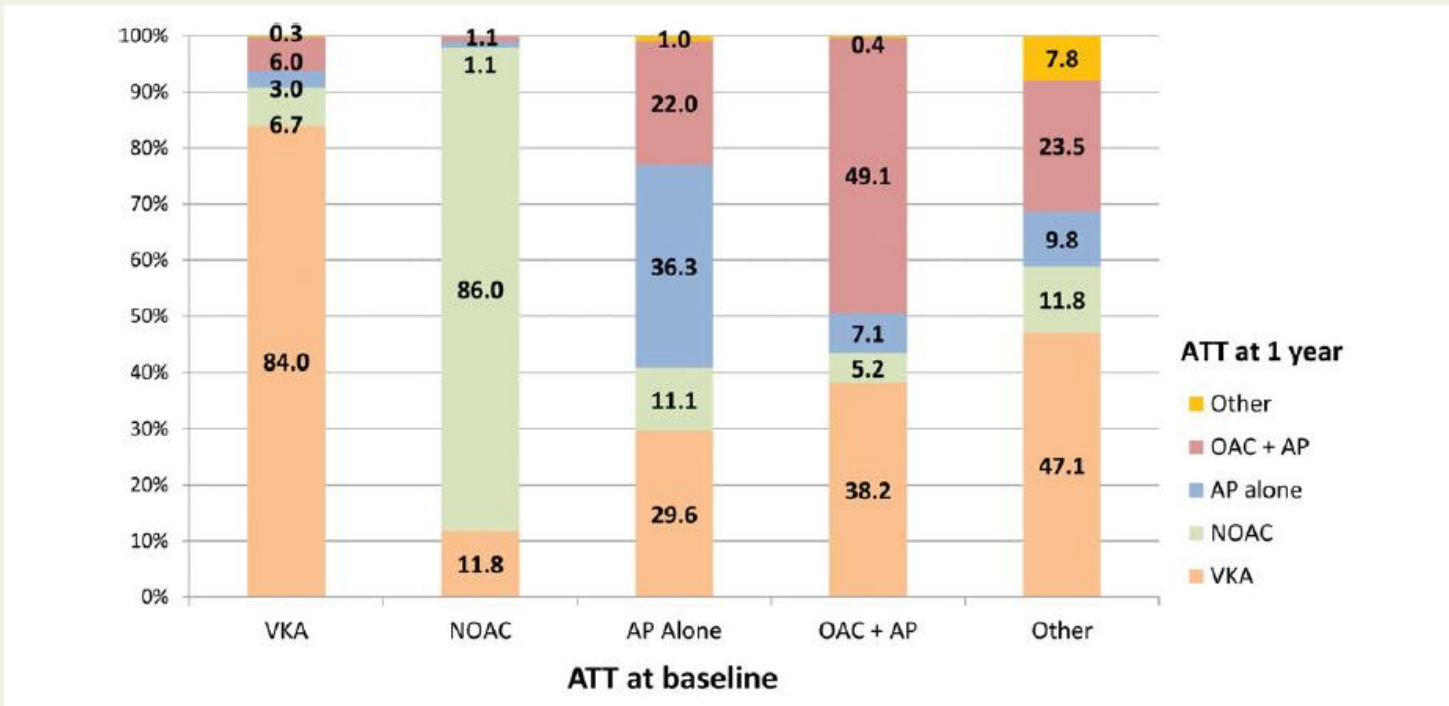

Figure 2 Antithrombotic therapy use at 1 year based on initial/baseline antithrombotic regimen. ATT, antithrombotic therapy; VKA, vitamin K antagonist; AP, antiplatelet therapy (most commonly aspirin); OAC, oral anticoagulant therapy.

Table 2 Drug therapies prescribed at follow-up

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
(a) Antithrombotic drugs by AF subgroup							
Oral anticoagulation drug (at least one OAC) (%)							
Pre-follow-up consultation	78.5 (1903/2423)	70.4 (496/705)	76.5 (509/665)	86.0 (449/522)	78.9 (90/114)	86.1 (359/417)	<0.0001*
After follow-up consultation	77.5 (1877/2423)	68.7 (484/705)	76.2 (507/665)	83.9 (438/522)	78.1 (89/114)	86.1 (359/417)	<0.0001*
VKA (%)							
Pre-follow-up consultation	68.1 (1650/2423)	59.7 (421/705)	65.6 (436/665)	74.5 (389/522)	73.7 (84/114)	76.7 (320/417)	<0.0001*
After follow-up consultation	66.4 (1610/2423)	58.2 (410/705)	64.2 (427/665)	71.5 (373/522)	71.9 (82/114)	76.3 (318/417)	<0.0001*
NOAC (at least one NOAC) (%)							
Pre-follow-up consultation	10.5 (255/2423)	10.8 (76/705)	11.1 (74/665)	11.7 (61/522)	5.3 (6/114)	9.1 (38/417)	0.2591*
After follow-up consultation	11.0 (267/2423)	10.5 (74/705)	12.3 (82/665)	12.3 (64/522)	6.1 (7/114)	9.6 (40/417)	0.2132*
Antiplatelet drug (at least one AP) (%)							
Pre-follow-up consultation	29.0 (703/2423)	31.5 (222/705)	27.1 (180/665)	27.8 (145/522)	45.6 (52/114)	24.9 (104/417)	0.0002*
After follow-up consultation	27.6 (669/2423)	29.8 (210/705)	25.7 (171/665)	26.2 (137/522)	43.0 (49/114)	24.5 (102/417)	0.0008*

	Total	Low	Moderate	High	*P*-value
(b) Antithrombotic therapy by stroke risk strata					
Oral anticoagulation drug (at least one OAC) (%)					
Pre-follow-up consultation	78.7 (1947/2475)	50.0 (109/218)	74.2 (204/275)	82.4 (1634/1982)	<0.0001*
After follow-up consultation	77.7 (1923/2475)	50.5 (110/218)	72.7 (200/275)	81.4 (1613/1982)	<0.0001*
VKA (%)					
Pre-follow-up consultation	68.2 (1688/2475)	42.7 (93/218)	59.3 (163/275)	72.3 (1432/1982)	<0.0001*
After follow-up consultation	66.6 (1649/2475)	40.4 (88/218)	58.2 (160/275)	70.7 (1401/1982)	<0.0001*
NOAC (at least one NOAC) (%)					
Pre-follow-up consultation	10.5 (261/2475)	7.8 (17/218)	14.9 (41/275)	10.2 (203/1982)	0.0237*
After follow-up consultation	11.1 (274/2475)	10.1 (22/218)	14.5 (40/275)	10.7 (212/1982)	0.1446*
Antiplatelet drug (at least one AP) (%)					
Pre-follow-up consultation	28.9 (715/2475)	14.7 (32/218)	19.3 (53/275)	31.8 (630/1982)	<0.0001*
After follow-up consultation	27.5 (680/2475)	15.1 (33/218)	16.7 (46/275)	30.3 (601/1982)	<0.0001*

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
(c) Rhythm/rate control drugs (at follow-up after consultation)							
Class Ia (quinidine) (%)	0.1 (2/2423)	0.1 (1/705)	0.0 (0/665)	0.2 (1/522)	0.0 (0/114)	0.0 (0/417)	0.8426*
Class Ic (flecainide or propafenone) (%)	9.3 (226/2423)	6.5 (46/705)	16.1 (107/665)	13.0 (68/522)	0.9 (1/114)	1.0 (4/417)	<0.0001*
Beta-blockers (%)	67.4 (1632/2423)	69.1 (487/705)	63.3 (421/665)	67.8 (354/522)	70.2 (80/114)	69.5 (290/417)	0.1220*
Class III (amiodarone or sotalol) (%)	22.7 (550/2423)	20.1 (142/705)	27.7 (184/665)	32.6 (170/522)	26.3 (30/114)	5.8 (24/417)	<0.0001*
Digitalis (mainly digoxin) (%)	49.0 (1188/2423)	49.8 (351/705)	35.8 (238/665)	49.6 (259/522)	63.2 (72/114)	64.3 (268/417)	<0.0001*

2.7% of patients at baseline were on no antithrombotic therapy.
P-values for among-group comparisons are from Pearson's χ^2 test.

Table 3 Interventions performed by 1-year follow-up

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
Pharmacological cardioversion (%)	5.1 (119/2344)	3.6 (25/692)	9.7 (63/647)	5.8 (28/485)	0.9 (1/111)	0.5 (2/409)	<0.0001*
Electrical cardioversion (%)	9.7 (232/2398)	8.0 (56/698)	11.1 (73/657)	16.7 (87/520)	9.7 (11/113)	1.2 (5/410)	<0.0001*
Catheter ablation (%)	4.4 (106/2405)	1.3 (9/700)	8.2 (54/661)	6.0 (31/520)	6.2 (7/113)	1.2 (5/411)	<0.0001*
Pacemaker implantation (%)	1.8 (44/2422)	1.3 (9/705)	2.3 (15/665)	2.5 (13/522)	0.0 (0/113)	1.7 (7/417)	0.2546*
Implantable defibrillator (%)	1.0 (24/2422)	1.1 (8/705)	0.8 (5/665)	0.8 (4/522)	0.9 (1/113)	1.4 (6/417)	0.7961*
AF surgery (%)	0.6 (14/2422)	0.4 (3/705)	0.9 (6/665)	0.8 (4/522)	0.9 (1/113)	0.0 (0/417)	0.2256*

ATT, antithrombotic therapy; VKA, vitamin K antagonist; AP, antiplatelet therapy (most commonly aspirin); OAC, oral anticoagulant therapy; NOAC, non-VKA oral anticoagulant.
**P*-values for among-group comparisons are from Pearson's χ^2 test.

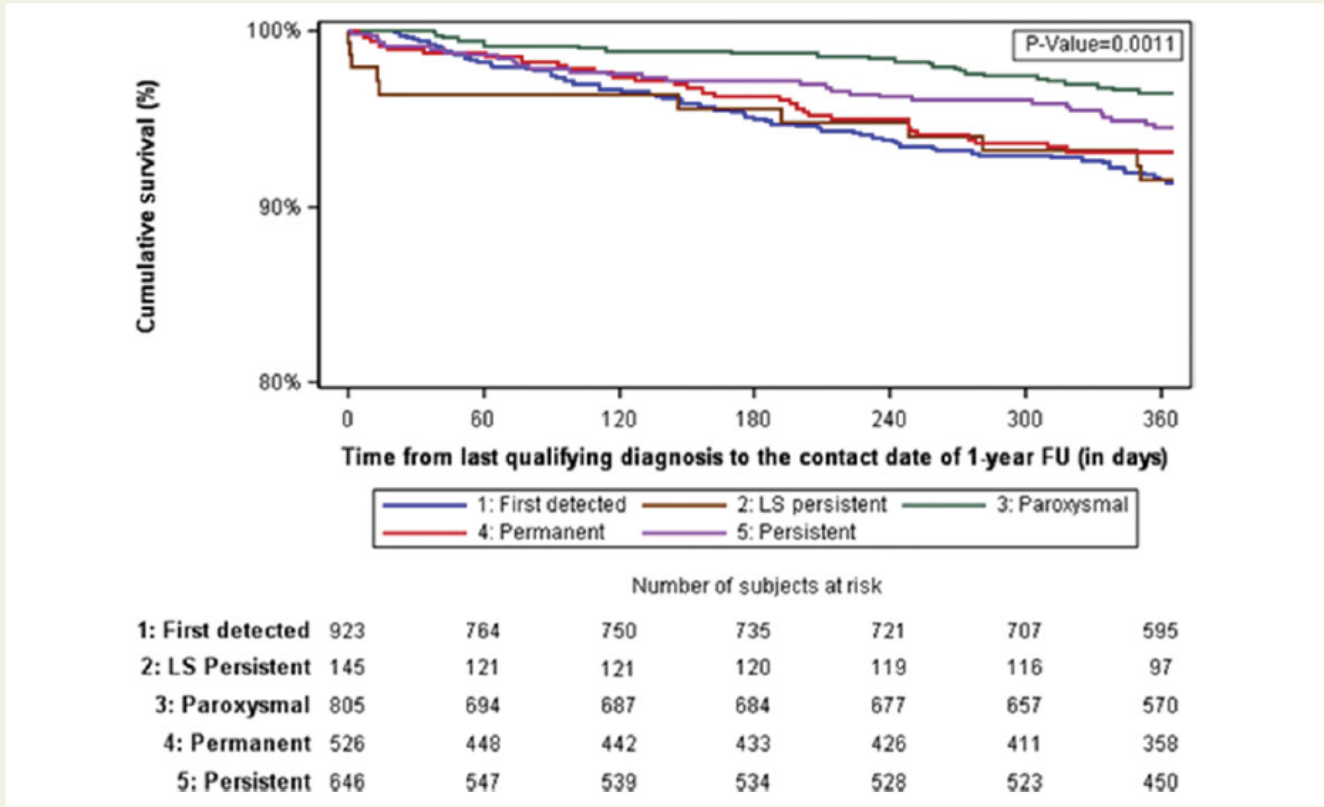

Figure 5 Kaplan–Meir curves for mortality in relation to atrial fibrillation subtype.

Table 4 Mortality and morbidity during the follow-up

	Total	First detected	Paroxysmal	Persistent	Long-standing persistent AF	Permanent	*P*-value
(a) Mortality (all)							
Death (%)	5.8 (176/3049)	7.5 (69/923)	3.5 (28/808)	4.9 (32/647)	8.3 (12/145)	6.7 (35/526)	0.0029*
Causes of death (details) (%)							
Cardiac	57.4 (66/115)	51.0 (25/49)	50.0 (9/18)	58.8 (10/17)	55.6 (5/9)	77.3 (17/22)	0.0288*
Vascular	13.0 (15/115)	8.2 (4/49)	22.2 (4/18)	11.8 (2/17)	44.4 (4/9)	4.5 (1/22)	
Non-cardiovascular	29.6 (34/115)	40.8 (20/49)	27.8 (5/18)	29.4 (5/17)	0.0 (0/9)	18.2 (4/22)	
Cardiac (%)							
Acute myocardial infarction	7.6 (5/66)	0.0 (0/25)	11.1 (1/9)	20.0 (2/10)	40.0 (2/5)	0.0 (0/17)	0.0186*
Heart failure	77.3 (51/66)	84.0 (21/25)	77.8 (7/9)	50.0 (5/10)	40.0 (2/5)	94.1 (16/17)	
Arrhythmia	7.6 (5/66)	8.0 (2/25)	11.1 (1/9)	10.0 (1/10)	20.0 (1/5)	0.0 (0/17)	
Other	7.6 (5/66)	8.0 (2/25)	0.0 (0/9)	20.0 (2/10)	0.0 (0/5)	5.9 (1/17)	
Vascular (%)							
Ischaemic stroke	20.0 (3/15)	0.0 (0/4)	0.0 (0/4)	0.0 (0/2)	50.0 (2/4)	100.0 (1/1)	0.5684*
Haemorrhagic stroke	53.3 (8/15)	75.0 (3/4)	50.0 (2/4)	50.0 (1/2)	50.0 (2/4)	0.0 (0/1)	
Pulmonary embolism	20.0 (3/15)	25.0 (1/4)	25.0 (1/4)	50.0 (1/2)	0.0 (0/4)	0.0 (0/1)	
Aorto-oesophageal fistula	6.7 (1/15)	0.0 (0/4)	25.0 (1/4)	0.0 (0/2)	0.0 (0/4)	0.0 (0/1)	
(b) Readmissions							
Readmission for AF/atrial flutter/atrial tachycardia (%)	17.9 (400/2238)	12.8 (87/679)	21.9 (137/627)	28.7 (137/477)	23.3 (17/73)	5.8 (22/382)	<0.0001*
Readmission: other cardiovascular events (%)	11.7 (265/2258)	15.1 (104/689)	7.4 (47/631)	10.2 (48/470)	10.5 (8/76)	14.8 (58/392)	0.0001*
ACS (%)	7.2 (19/264)	4.8 (5/104)	21.3 (10/47)	4.2 (2/48)	0.0 (0/7)	3.4 (2/58)	0.0098*
Heart failure (%)	42.8 (113/264)	42.3 (44/104)	29.8 (14/47)	35.4 (17/48)	28.6 (2/7)	62.1 (36/58)	0.0083*
Coronary intervention (%)	20.1 (53/264)	21.2 (22/104)	34.0 (16/47)	18.8 (9/48)	14.3 (1/7)	8.6 (5/58)	0.0298*
Arrhythmia, other than AF/atrial flutter (%)	11.0 (29/264)	8.7 (9/104)	12.8 (6/47)	18.8 (9/48)	28.6 (2/7)	5.2 (3/58)	0.0950*
Cardiac arrest (%)	1.5 (4/264)	2.9 (3/104)	0.0 (0/47)	2.1 (1/48)	0.0 (0/7)	0.0 (0/58)	0.6171*
Stroke (%)	5.7 (15/264)	6.7 (7/104)	4.3 (2/47)	4.2 (2/48)	0.0 (0/7)	6.9 (4/58)	0.9450*
TIA (%)	2.3 (6/264)	0.0 (0/104)	4.3 (2/47)	4.2 (2/48)	14.3 (1/7)	1.7 (1/58)	0.0277*
Peripheral embolism (%)	1.1 (3/263)	1.0 (1/104)	0.0 (0/46)	0.0 (0/48)	0.0 (0/7)	3.4 (2/58)	0.4025*
Non-cardiovascular events (%)	12.6 (286/2261)	13.3 (90/678)	12.8 (81/635)	11.1 (52/467)	8.1 (7/86)	14.2 (56/395)	0.4579*
Bleeding (%)	8.4 (24/286)	11.1 (10/90)	2.5 (2/81)	9.6 (5/52)	14.3 (1/7)	10.7 (6/56)	0.1304*

ACS, acute coronary syndrome; TIA, transient ischaemic attack.
*P-values for among-group comparisons are from Pearson's χ^2 test.

Table 5 Multivariate analysis

Clinical variable	Odds ratio estimates			
	Point estimate	95% CI		*P*-value
(a) Stroke/TIA/peripheral embolism and/or mortality				
Age	1.063	1.043	1.081	<0.0001
AF as primary reason for admission/ consultation	2.439	1.600	3.353	<0.0001
Chronic heart failure	2.046	1.377	2.890	0.0001
Previous TIA	2.366	1.392	4.395	0.0033
Chronic kidney disease	2.690	1.947	3.965	<0.0001
Malignancy	1.770	1.008	3.107	0.0467
Bleeding	1.965	1.146	3.368	0.0141
(b) Mortality				
Age	1.060	1.040	1.081	<0.0001
AF as reason for admission/ consultation	2.716	1.820	4.055	<0.0001
Previous TIA	2.371	1.301	4.321	0.0048
Chronic kidney disease	3.325	2.293	4.822	<0.0001
Chronic obstructive pulmonary disease	1.647	1.068	2.541	0.0241
Malignancy	1.816	1.007	3.276	0.0474
Bleeding	2.248	1.287	3.929	0.0044
Diuretics	1.712	1.126	2.604	0.0119
Statins	0.645	0.452	0.919	0.0153

AF, atrial fibrillation; TIA, transient ischaemic attack.

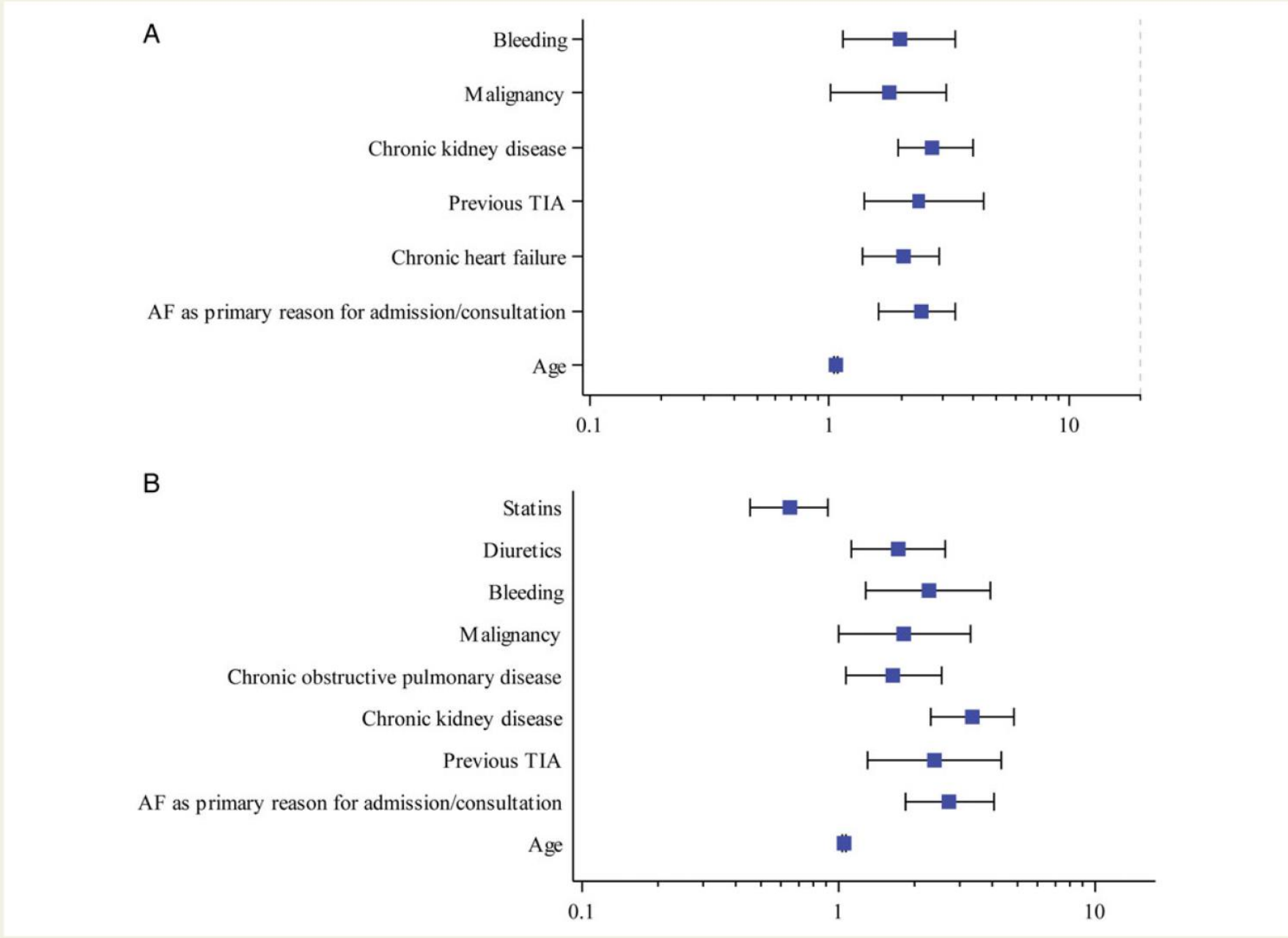

Figure 6 Forest plots showing odds ratios (and 95% CIs) for multivariate predictors of stroke/transient ischaemic attack/peripheral embolism and/or mortality. (*A*) Stroke/transient ischaemic attack/peripheral embolism and/or mortality. (*B*) All-cause mortality.

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Review

Antiarrhythmic drugs for the maintenance of sinus rhythm: Risks and benefits

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British Heart Foundation Professor Clinical Cardiology, St. George's, University of London, Department of Cardiological Sciences, London, United Kingdom

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice, and its complications impose a significant economic burden. The development of more effective agents to manage patients with AF is essential. While clinical trials show no major differences in outcomes between rate and rhythm control strategies, some patients with AF require treatment with antiarrhythmic drugs (AADs) to maintain sinus rhythm, reduce symptoms, improve exercise tolerance, and improve quality of life. Currently available AADs, while effective, have limitations including limited efficacy, adverse events, toxicity, and proarrhythmic potential. The 6 most commonly used AADs (amiodarone, disopyramide, dofetilide [USA but not Europe], flecainide, propafenone, sotalol) have proarrhythmic effects (fewer with amiodarone). Amiodarone is the most effective AAD, but its safety profile limits its usefulness. Recent advances in AAD therapy include dronedarone and vernakalant. Dronedarone, approved by the United States Food and Drug Administration and the European Medicines Authority and others, has been proven efficacious in maintaining sinus rhythm and reducing the incidence of hospitalization due to cardiovascular events or death in patients with AF. The intravenous formulation of vernakalant is approved in the European Union, Iceland, and Norway. Oral vernakalant is currently undergoing evaluation for preventing AF recurrence and appears to be effective with an acceptable safety profile. Treatment should be individualized to the patient with consideration of pharmacologic risks and benefits according to AF management guidelines. Accumulating efficacy and safety data for new and emerging AADs holds promise for improved AF management and outcomes.

Table 1
The Vaughan Williams classification of antiarrhythmic drugs.
Adapted from Antiarrhythmics—from cell to clinic: past, present, and future, Hancox JC, Patel KC, Jones JV, Heart 84:14–24, ©2000 with permission from BMJ Publishing Group Ltd.

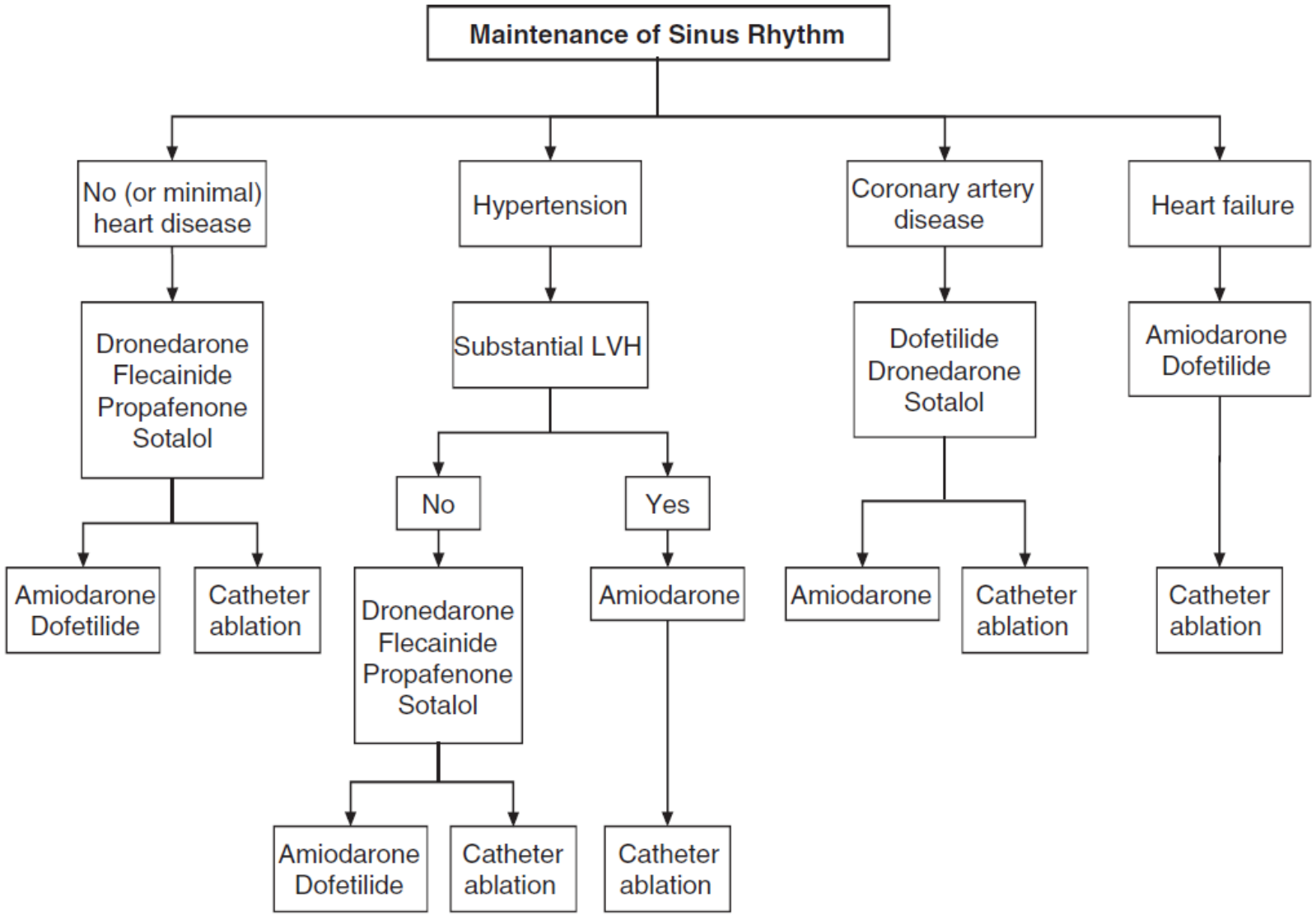
Class	Basic mechanism	AADs
I: Sodium channel blockade	IA: • Slow dV/dt of phase 0 • Moderate prolongation of repolarization and PR and QRS duration	• Disopyramide • Procainamide • Quinidine
	IB: • Limited effect on dV/dt • Shortens repolarization and hence QT interval	• Lidocaine • Mexiletine
	IC: • Slows dV/dt • Little effect on repolarization • Marked prolongation of PR and QRS intervals	• Flecainide • Propafenone
II: Beta blockade	• Blocks sympathetic activity • Slow rate of rise of phase 4 of the action potential and thus slow discharge of the SAN and AVN	• Atenolol • Metoprolol • Bisoprolol • Sotalol • Carvedilol
III: Potassium channel blockade	• Increases APD by blocking the delayed rectifier current and generally reduces automaticity • SAN and AVN rates slightly suppressed	• Amiodarone • Dofetilide • Ibutilide • Sotalol
IV: Calcium channel blockade	• Blocks L-type calcium-channels • Depresses phase 2 and 3 of the action potential by blocking the slow Ca current	• Verapamil • Diltiazem

APD, action potential duration; AVN, atrioventricular node; SAN, sino-atrial node.

Table 2
Efficacy, adverse events, and contraindications of antiarrhythmic drugs used for maintenance of sinus rhythm.

Drug	Efficacy [27]	Most common adverse events	Contraindications
Amiodarone[a][34]	50–78%	• Nausea/vomiting • Photosensitivity • Visual disturbances • Abnormal liver function tests • Pulmonary fibrosis	• Severe sinus node dysfunction causing marked sinus bradycardia • 2nd- or 3rd-degree AV block • Episodes of bradycardia causing syncope (except when used in conjunction with a pacemaker) • Hypersensitivity to iodine
Disopyramide[a][28]	44–54%	• Urinary retention • Dry mouth • Constipation • Blurred vision	• 2nd- or 3rd-degree AV block (unless functional pacemaker present) • Congenital QT prolongation • Cardiogenic shock
Dofetilide [33]	66–71%	• Headache • Chest pain • Dizziness • Respiratory tract infection • Dyspnea	• Congenital or acquired long QT syndromes • Severe renal impairment • concomitant use with verapamil, cimetidine, trimethoprim, ketoconazole, or hydrochlorothiazide
Dronedarone [35]	33–39%	• Diarrhea • Nausea • Abdominal pain • Vomiting • Asthenia	• NYHA class IV heart failure • NYHA class II–III heart failure with recent decompensation • 2nd- or 3rd-degree AV block or sick sinus syndrome • Bradycardia • Concomitant use of strong CYP3A4 inhibitors • Concomitant use of drugs that prolong the QT interval and may induce torsades de pointes • Severe hepatic impairment • QTc Bazett interval ≥500 ms
Flecainide [30]	34–42%	• CHF • Ventricular tachycardia • Dizziness • Visual disturbances	• 2nd- or 3rd-degree AV block • Right bundle branch block associated with left hemiblock • Cardiogenic shock
Propafenone [31]	35–40%	• Dizziness • Nausea/vomiting • Unusual taste • Constipation	• Uncontrolled congestive heart failure • Cardiogenic shock • Sinoatrial, atrioventricular, and intraventricular disorders of impulse generation and/or conduction in absence of artificial pacemaker • Bradycardia • Marked hypotension • Bronchospastic disorders • Electrolyte imbalances
Quinidine [29]	23–58%	• Diarrhea • Nausea/vomiting • Heartburn/esophagitis	• Thrombocytopenic purpura • Patients whose cardiac rhythm is dependent on a junctional or idioventricular pacemaker in the absence of a functioning artificial pacemaker • Patients who cannot receive anticholinergic agents
Sotalol [32]	37–50%	• Dyspnea • Fatigue • Dizziness • Bradycardia • Chest pain	• Bronchial asthma • Sinus bradycardia • 2nd- or 3rd-degree AV block (unless functional pacemaker present) • Congenital or acquired long QT syndromes • Cardiogenic shock • Uncontrolled CHF
Vernakalant[b][36]	61%	• Not available	• Not available

AV, atrioventricular; CHF, congestive heart failure; NYHA, New York Heart Association.
[a] Not approved by the US Food and Drug Administration for atrial fibrillation.
[b] Currently undergoing evaluation for preventing AF recurrence; data from phase 2a study.


Maintenance of Sinus Rhythm
No (or minimal) heart disease
Hypertension
Coronary artery disease
Heart failure
Dronedarone Flecainide Propafenone Sotalol
Substantial LVH
Dofetilide Dronedarone Sotalol
Amiodarone Dofetilide
No
Yes
Amiodarone Dofetilide
Catheter ablation
Dronedarone Flecainide Propafenone Sotalol
Amiodarone
Amiodarone
Catheter ablation
Catheter ablation
Amiodarone Dofetilide
Catheter ablation
Catheter ablation

Original Article

Comparisons of Hospitalization Rates Among Younger Atrial Fibrillation Patients Receiving Different Antiarrhythmic Drugs

Nancy M. Allen LaPointe, PharmD, MHS; David Dai, PhD, MS; Laine Thomas, PhD; Jonathan P. Piccini, MD, MHS; Eric D. Peterson, MD, MPH; Sana M. Al-Khatib, MD, MHS

Background—Antiarrhythmic drugs (AADs) are used to reduce the frequency, severity, and duration of atrial fibrillation (AF) events, which should reduce hospitalizations; however, little is known about the associations between different AADs and hospitalization—particularly among younger AF patients without structural heart disease.

Methods and Results—Using MarketScan® claims data, we identified AF patients without coronary artery disease or heart failure who received their first AAD prescription (amiodarone, sotalol, dronedarone, or Class Ic) within 14 days post-first AF encounter. The primary outcome was time from first AAD prescription to AF hospitalization, and secondary outcomes included time to cardiovascular and all-cause hospitalizations. We used inverse probability-weighted estimators to adjust for differences in treatment allocation in the Cox proportional hazards model for each outcome. Among 8562 AF patients with a median age of 56 years (interquartile range 49, 61), risk of AF hospitalization was greater with dronedarone than Class Ic (hazard ratio [HR] 1.59; 95% confidence interval 1.13–2.24), amiodarone (HR 2.63; 1.77–3.89), and sotalol (HR 1.72; 1.17–2.54), but lower with amiodarone versus Class Ic (HR 0.68; 0.57–0.80) and sotalol (HR 0.63; 0.53–0.75). Risk of cardiovascular hospitalization was lower with amiodarone than Class Ic (HR 0.80; 0.70–0.92), but not non-AF cardiovascular hospitalization (HR 1.26; 1.01–1.57). There was no difference in all-cause hospitalization between amiodarone, Class Ic, and sotalol.

Conclusions—Differences in hospitalization rates were found between AADs in younger AF patients without structural heart disease. Amiodarone had the lowest risk of AF hospitalization and dronedarone had the greatest risk. Additional research is needed to better understand associations between AADs and hospitalization risk. (***Circ Cardiovasc Qual Outcomes*. 2015;8:00-00. DOI: 10.1161/CIRCOUTCOMES.114.001499.**)

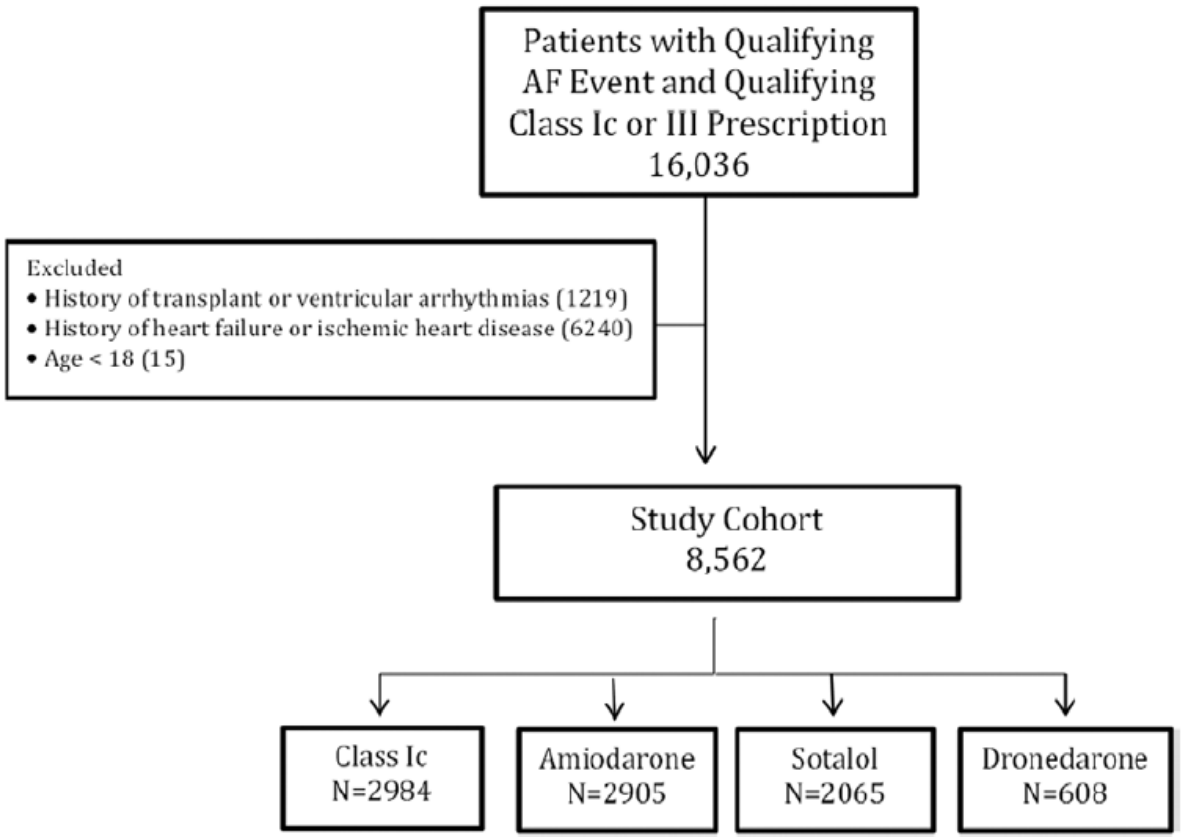


Figure 1. Study cohort. This figure displays the final study cohort, from the initial patient population through exclusions. AF indicates atrial fibrillation.

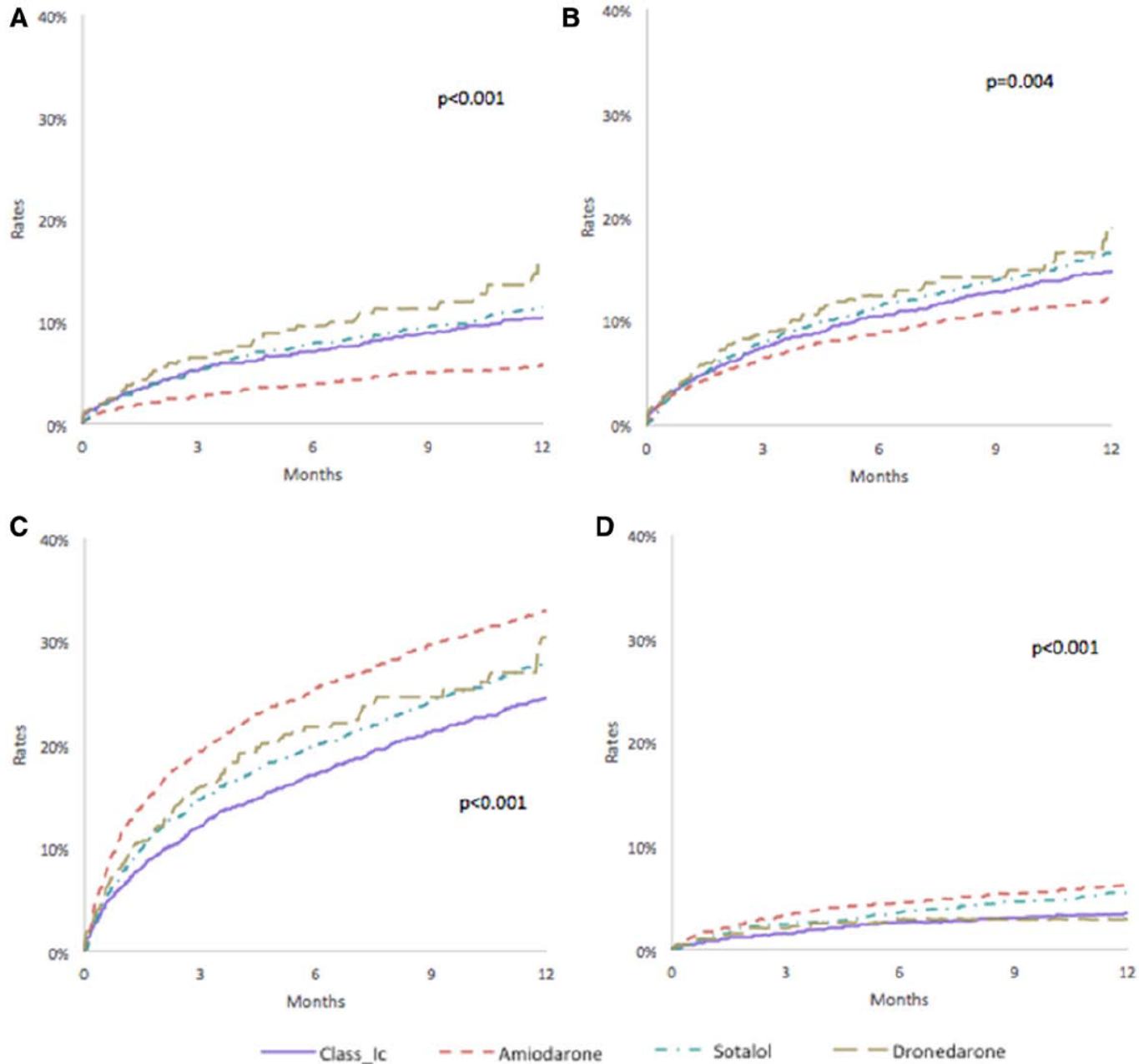


Figure 2. Kaplan–Meier rates of hospitalization type. This figure displays the Kaplan–Meier rates of AF hospitalization (**A**); cardiovascular hospitalization (**B**); all-cause hospitalization (**C**); and non-AF/atrial flutter cardiovascular hospitalization (**D**), according to the following AAD treatment groups: Class Ic, amiodarone, sotalol, and dronedarone. AAD indicates antiarrhythmic drug; AF, atrial fibrillation.

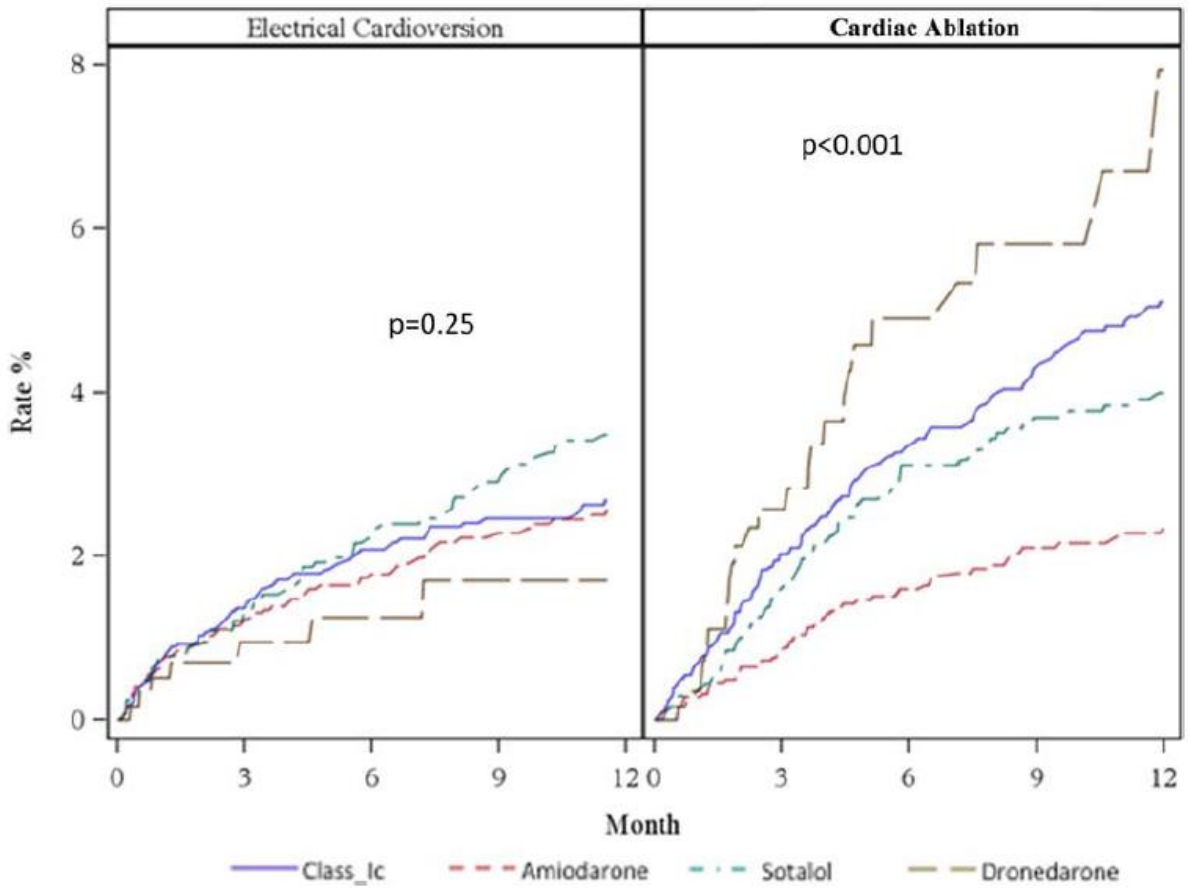


Figure 3. Kaplan–Meier rates of electric cardioversions and cardiac ablation. This figure displays Kaplan–Meier rates of electric cardioversions and cardiac ablation according to the following AAD treatment groups: Class 1c, amiodarone, sotalol, and dronedarone. AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AFA, atrial fibrillation ablation.

Propafenone

The dosage of propafenone needs to be reduced in patients with severe hepatic and renal insufficiency.

CYP2D6 is genetically absent in 7% of the patients (poor metabolizers) and is inhibited by tricyclic antidepressants, fluoxetine, and quinidine. These drug interactions and genetic poor metabolism can lead to excess drug levels and enhance b-blocker and calcium channel blocker properties of parent propafenone

요양급여 의 뢰 서

보험자기호	00000000000	보험자명칭		건강보험증번호 (세대관리번호)	71307062999
피보험자성명 (세대주성명)	맹우민	주민등록번호			
수진자성명	김정순	주민등록번호	480125-2841319		
수진자주소	경남 창원시 진해구 경화동 1172-5				
상 병 명	심방세동				
진 료 기 간	2012-04-12 ~ 2012-04-12			진 료 구 분	입원
전원기관명	고신대학병원			전 원 사 유	특수 검사 및 진단

환 자 상 태 및

차태준 교수님, 안녕하세요?

고혈압 환자로 10년 전부터 돌발적으로 가슴 뛰는 증세 있어서
돌발성 심방세동으로 수차례 입원치료한 환자입니다.

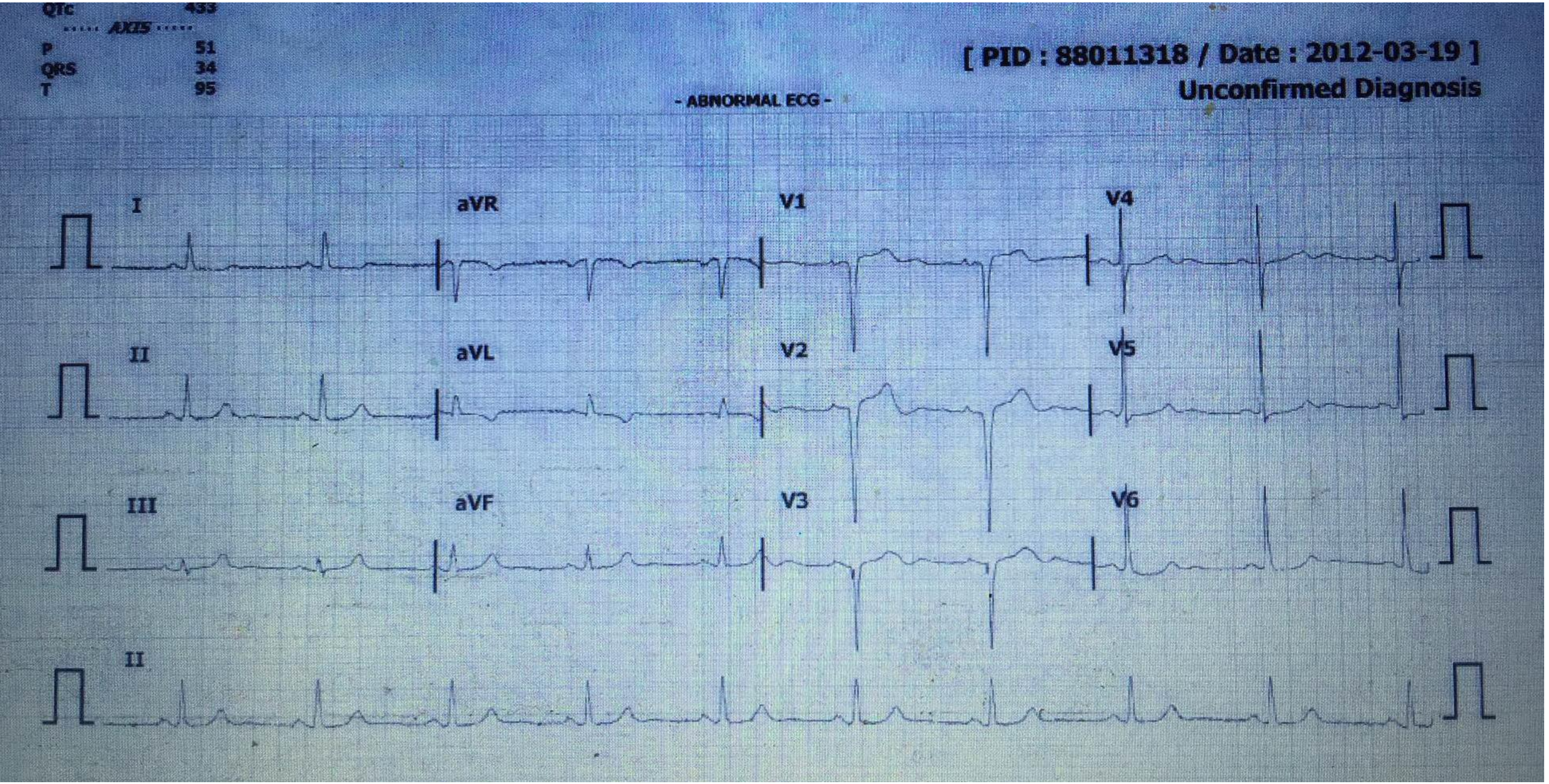
베타 차단제, Propafenone 투여중에 최근 증상 자주 발생하여
RFCA 필요할 것으로 사료됩니다.
(Propafenone 은 최근 QRS widening 있어 중단 하였습니다.)

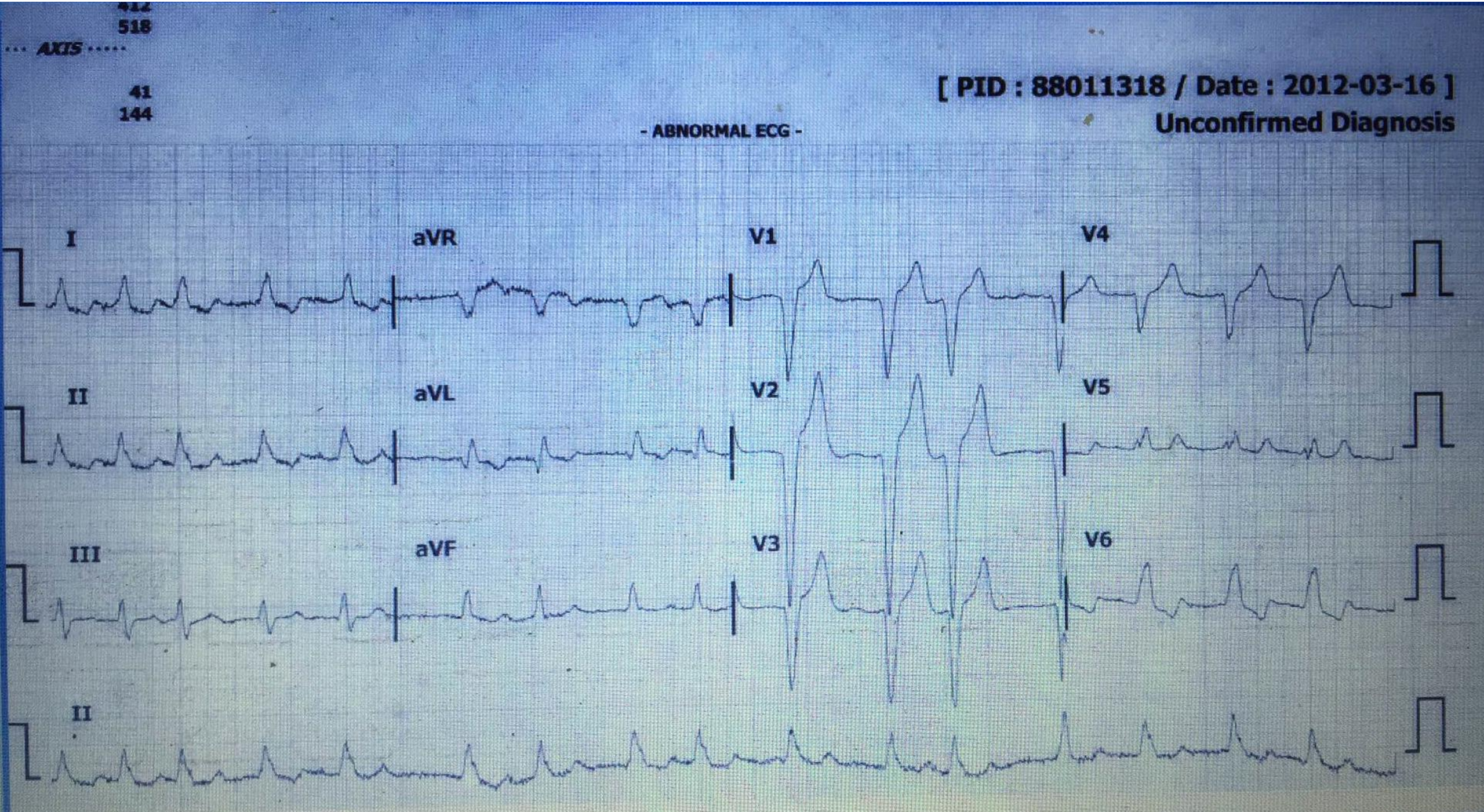
2010년 CAG 에서는 특이소견 없었습니다.

의뢰드리오니 고진선처 바랍니다.

※ 환자의 요구가 있는 경우에는 일반의약품으로 처방할 수 있습니다.

처방의약품의 명칭	1회 투약량	1일 부여횟수	총 투약일수	용법
1 아스피린프로텍트정 100mg-Aspirin protect 100mg(바이엘)	1 TAB	2	56	1일2회 아침, 저녁식후 30분
2 콩코르정 5mg-Concor tab 5mg★(한국머크)	1 tab	2	56	〃
3 리트모놈정150mg-Rytmonorm 150mg(일성신약)	1 TAB	2	56	〃
4 코자정-Cozaar 50mg★(MSD)	1 TAB	1	56	1일1회 아침식후 30분
5 리바로정 2mg-Livalo 2mg(중외제약)	1 Tab	1	56	1일1회 저녁식후 30분
6 알프람정0.25mg-Alpram 0.25mg★(환인제약)	1 Tab	4	28	의사지시대로 복용


QTc 433
AXIS
P 51
QRS 34
T 95
[PID : 88011318 / Date : 2012-03-19]
Unconfirmed Diagnosis
- ABNORMAL ECG -
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II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518
··· AXIS ·····
41
144
[PID : 88011318 / Date : 2012-03-16]
- ABNORMAL ECG -
Unconfirmed Diagnosis
I
aVR
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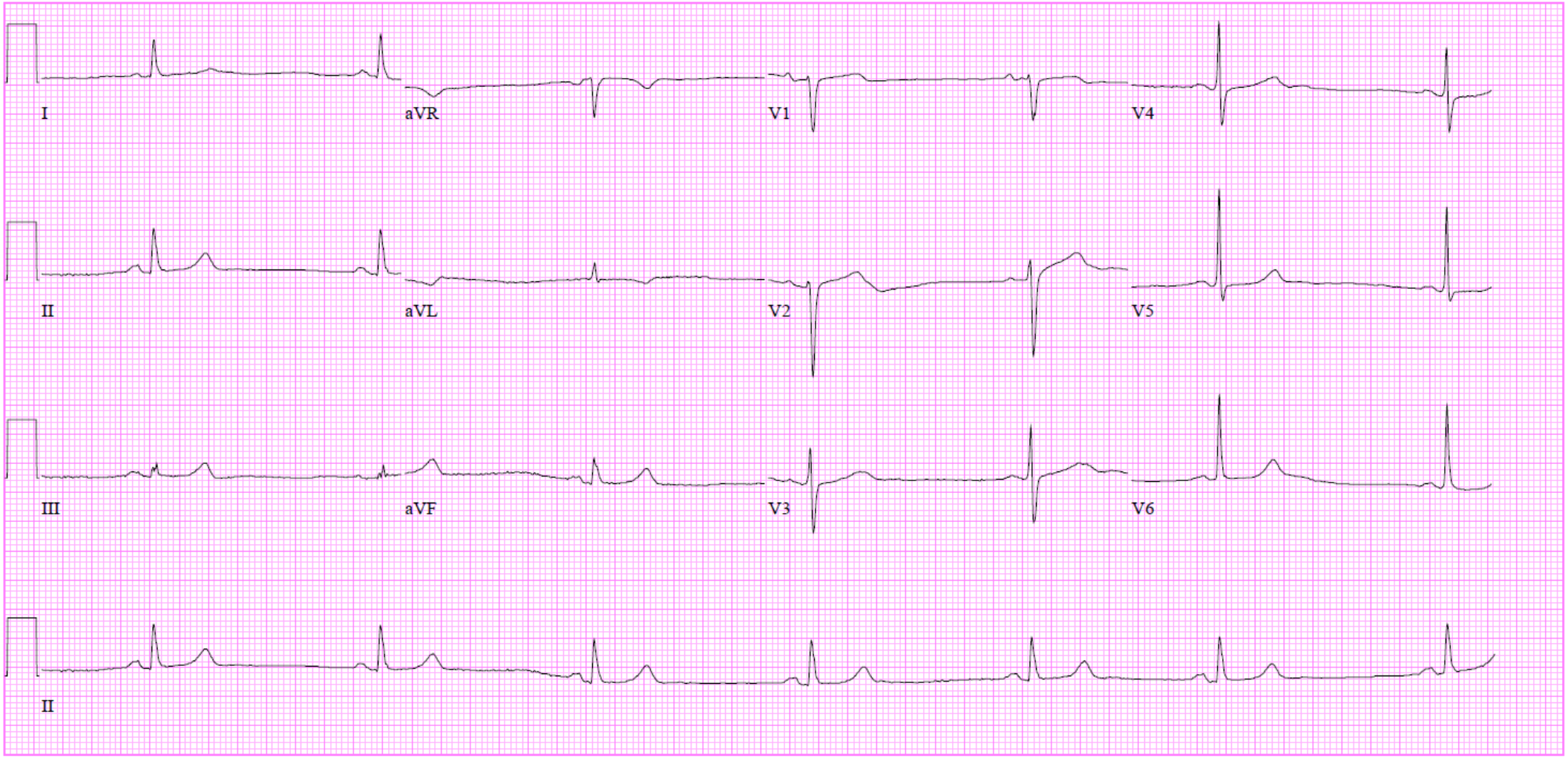
aVL
V2
V5
III
aVF
V3
V6
II

Propafenone induced LBBB in paroxysmal AF



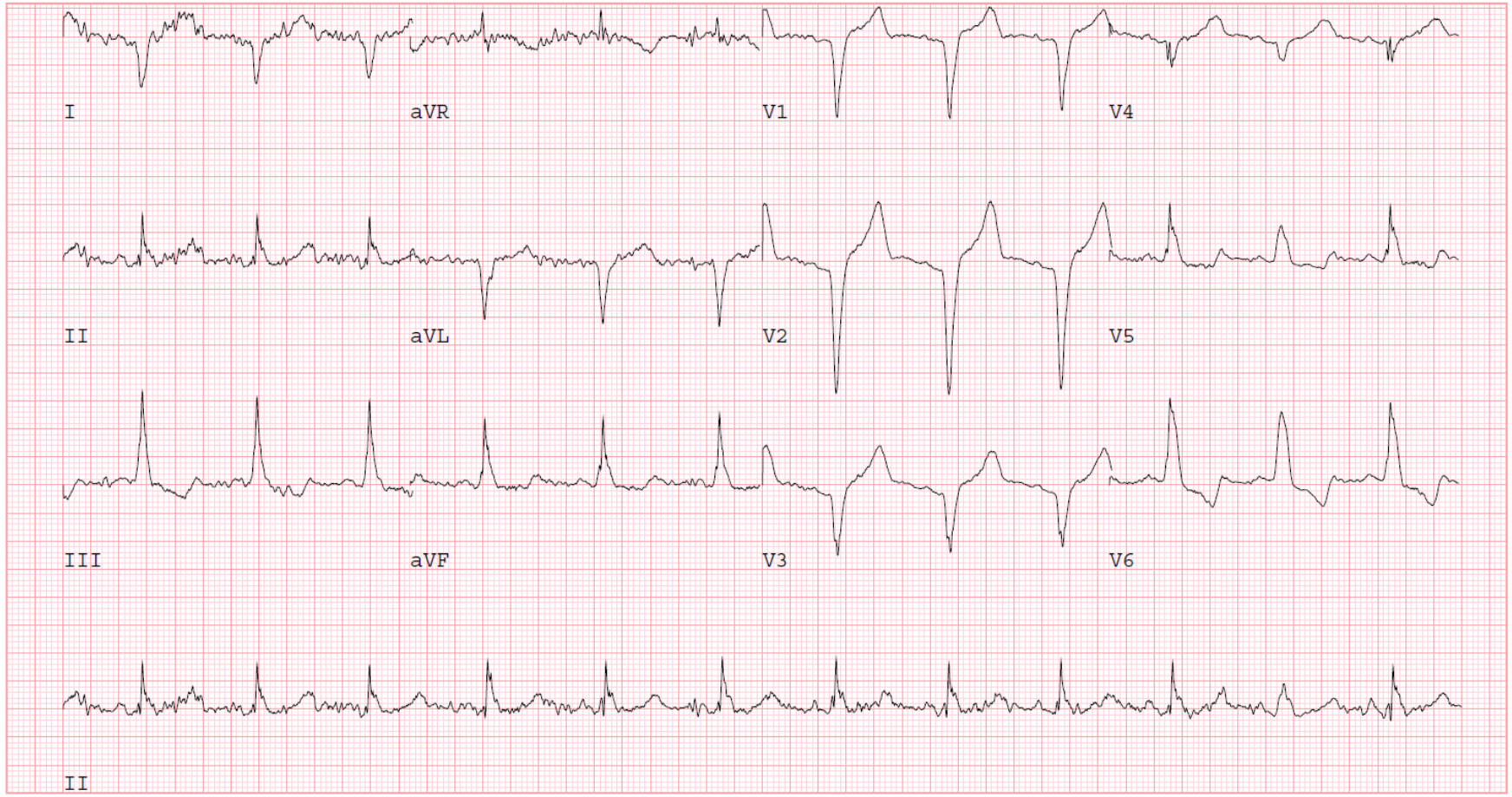
TMT test at stage 1 of bruce protocol

Kim, Jeongsun
Patient ID1207506
2012/04/17
4:47:58pm

71 bpm

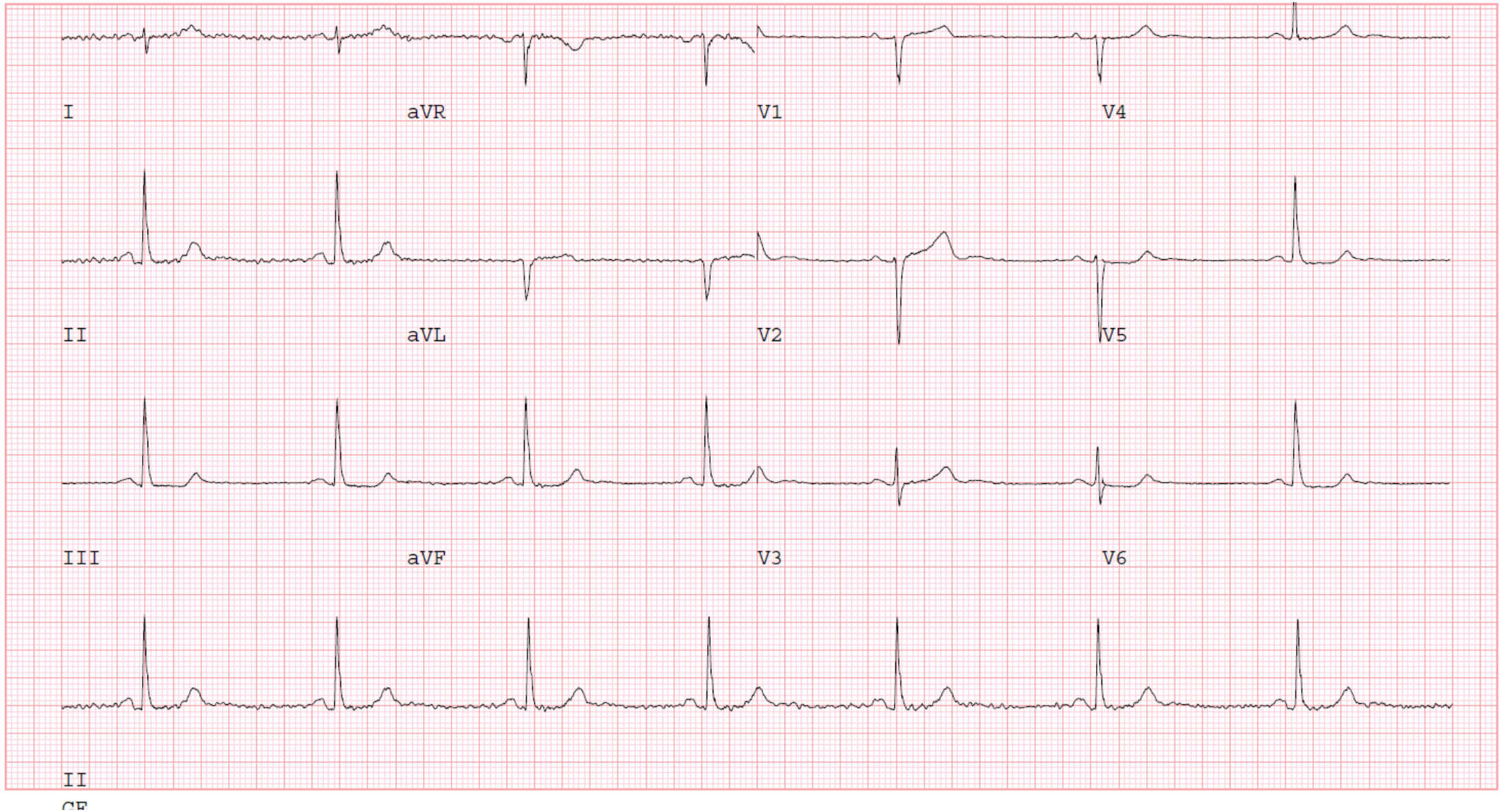
EXERCISE
STAGE 1
01:25

BRUCE
2.7 km/h
10.0 %



GE

Post AF ablation (2012/April/18 ablation)



Flecainide

- The risk of cardiovascular side effects increases at higher drug plasma levels, and the probability of a cardiovascular event begins to rise sharply at increases of approximately 40 ms in both PR and QRS intervals from baseline. These results confirmed that flecainide dosing is complicated by the steepness of the dose–response for both safety and efficacy.

Eur J Clin Pharmacol (2015) 71:549–567
DOI 10.1007/s00228-015-1832-0

REVIEW ARTICLE

Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide

Juan Tamargo · Jean-Yves Le Heuzey · Phillipe Mabo

Received: 5 December 2014 / Accepted: 4 March 2015 / Published online: 15 April 2015

Abstract
Purpose The therapeutic index (TI) is the range of doses at which a medication is effective without unacceptable adverse events. Drugs with a narrow TI (NTIDs) have a narrow window between their effective doses and those at which they produce adverse toxic effects. Generic drugs may be substituted for brand-name drugs provided that they meet the recommended bioequivalence (BE) limits. However, an appropriate range of BE for NTIDs is essential to define due to the potential for ineffectiveness or adverse events. Flecainide is an antiarrhythmic agent that has the potential to be considered an NTID. This review aims to evaluate the literature surrounding guidelines on generic substitution for NTIDs and to evaluate the evidence for flecainide to be considered an NTID.
Methods A review of recommendations from various regulatory authorities regarding BE and NTIDs, and publications regarding the NTID characteristics of flecainide, was carried out.
Results Regulatory authorities generally recommend reduced BE limits for NTIDs. Some, but not all, regulatory authorities specify flecainide as an NTID. The literature review demonstrated that flecainide displays NTID characteristics including a steep drug dose–response relationship for safety and efficacy, a need for therapeutic drug monitoring of pharmacokinetic (PK) or pharmacodynamics measures and intra-subject variability in its PK properties.
Conclusions There is much evidence for flecainide to be considered an NTID based on both preclinical and clinical data. A clear understanding of the potential of proarrhythmic effects or lack of efficacy, careful patient selection and regular monitoring are essential for the safe and rational administration of flecainide.

Keywords Antiarrhythmic drugs · Flecainide · Generic drugs · Bioequivalence · Narrow therapeutic index · Safety

Table 1 Different opinions on the BE of NTIDs with a particular interest in flecainide

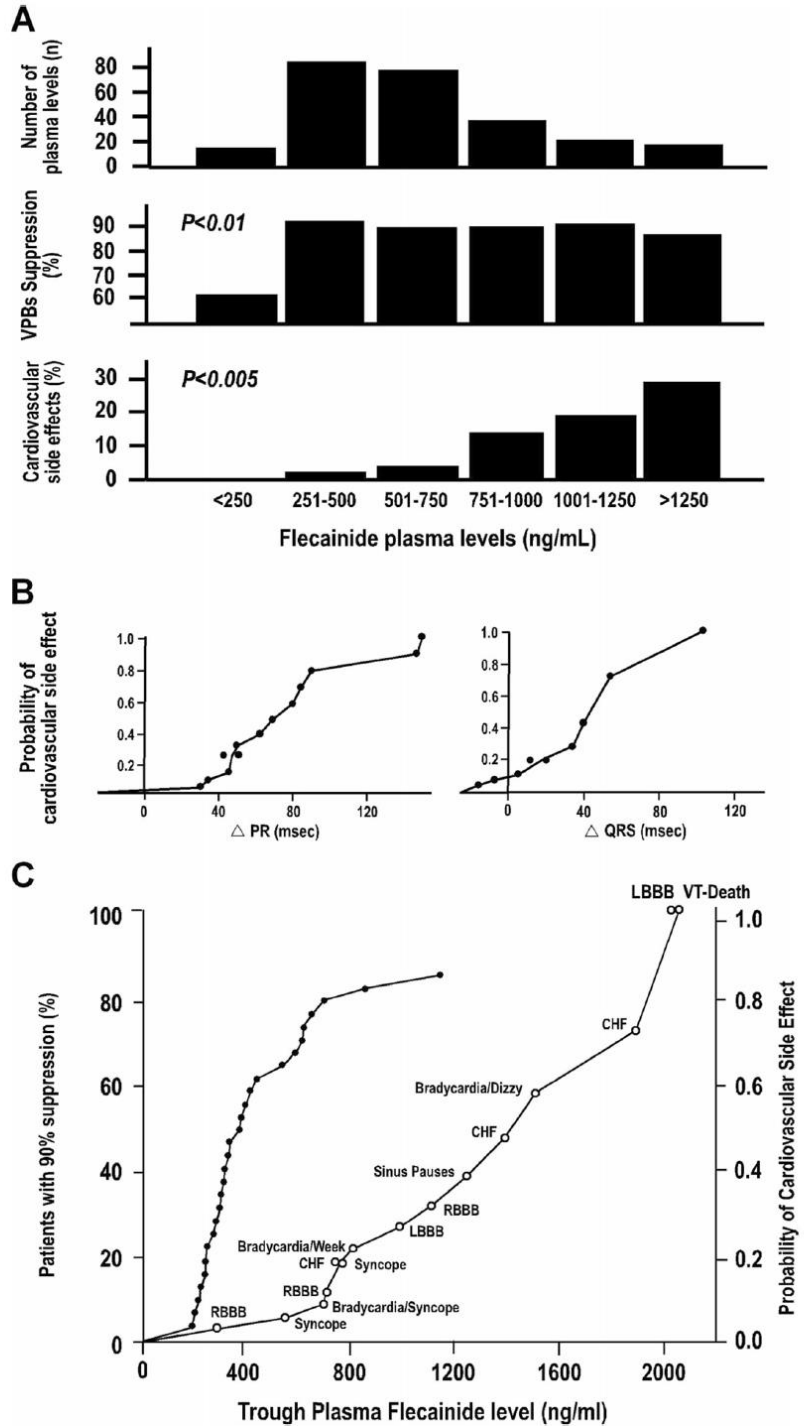
Agency	BE criteria for general drugs	BE criteria for NTID	Flecainide as an NTID
Foods and Drug Administration (FDA)	80.00–125.00 %	90.00–111.11 %	No
European Medicines Agency (EMA)	80.00–125.00 %	90.00–111.11 %	No
Danish Health and Medicines Authority	80.00–125.00 %	90.00–111.11 %	The agency tightened the BE limits for AADs
Federal Agency for Medicines and Health Products (FAMHP) of Belgium	80.00–125.00 %	90.00–111.11 %	
Health Protection and Food Branch (HPFB) of Canada	80.00–125.00 %	90.00–112.00 %	Flecainide is considered a critical dose drug
New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE)	80.00–125.00 %		Yes
Japanese Institute of Health Sciences (NIHS)	80.00–125.00 %	90.00–111.11 %	Digoxin, disopyramide and quinidine, but not flecainide
Medicines Control Council (MCC) of South Africa	80.00–125.00 %	Tighter limits are considered for NTID	AADs are considered NTID
Therapeutic Goods Administration of Australia (TGA)	80.00–125.00 %	90.00–111.11 %	No list of NTID
Agence Fédérale des Médicaments et des Produits de Santé of Belgium		90.00–111.11 %	Yes
French Agence Nationale de Sécurité des Médicaments (ANSM)			Yes
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	80.00–125.00 %	90.00–111.11 %	Yes

AADs antiarrhythmic drugs, *BE* bioequivalence, *NTIDs* narrow therapeutic index drugs

Table 2 Flecainide presents the pharmacological profile of an NTID

NTI characteristics of flecainide
Steep concentration–response relationships for efficacy, toxicity or both in the usual dosing interval [46, 49, 53, 54, 59, 96]
Dosing generally needs to be titrated according to clinical response [43, 44, 47]
Small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions [43, 49, 54]
There may be a potential for serious clinical consequences in the event of too low or high concentrations [43, 45, 47, 53, 59]
Periodic monitoring of plasma levels is required in patients with severe renal failure or severe hepatic disease [52]
Drug overdose with flecainide is frequently fatal [43, 47, 52, 137]

NTID narrow therapeutic index drug


A
Number of plasma levels (n)
80
60
40
20
0
VPBs Suppression (%)
P<0.01
90
80
70
60
Cardiovascular side effects (%)
P<0.005
30
20
10
0
<250
251-500
501-750
751-1000
1001-1250
>1250
Flecainide plasma levels (ng/mL)
B
Probability of cardiovascular side effect
1.0
0.8
0.6
0.4
0.2
0
40
80
120
△ PR (msec)
△ QRS (msec)
C
Patients with 90% suppression (%)
100
80
60
40
20
0
400
800
1200
1600
2000
Trough Plasma Flecainide level (ng/ml)
Probability of Cardiovascular Side Effect
1.0
0.8
0.6
0.4
0.2
0.0
LBBB VT-Death
CHF
Bradycardia/Dizzy
CHF
Sinus Pauses
RBBB
LBBB
Bradycardia/Week
CHF
Syncope
RBBB
Bradycardia/Syncope
RBBB
Syncope

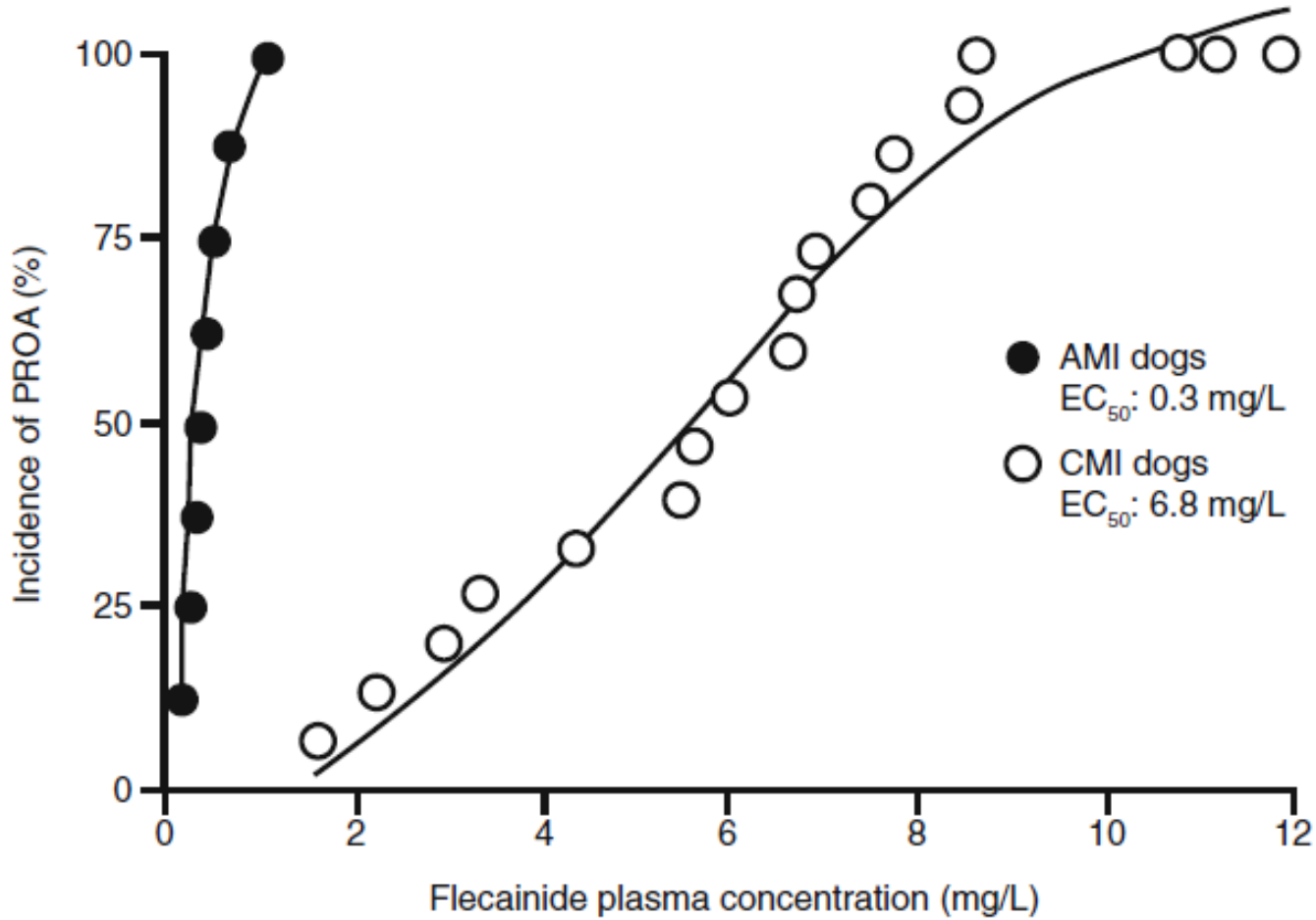


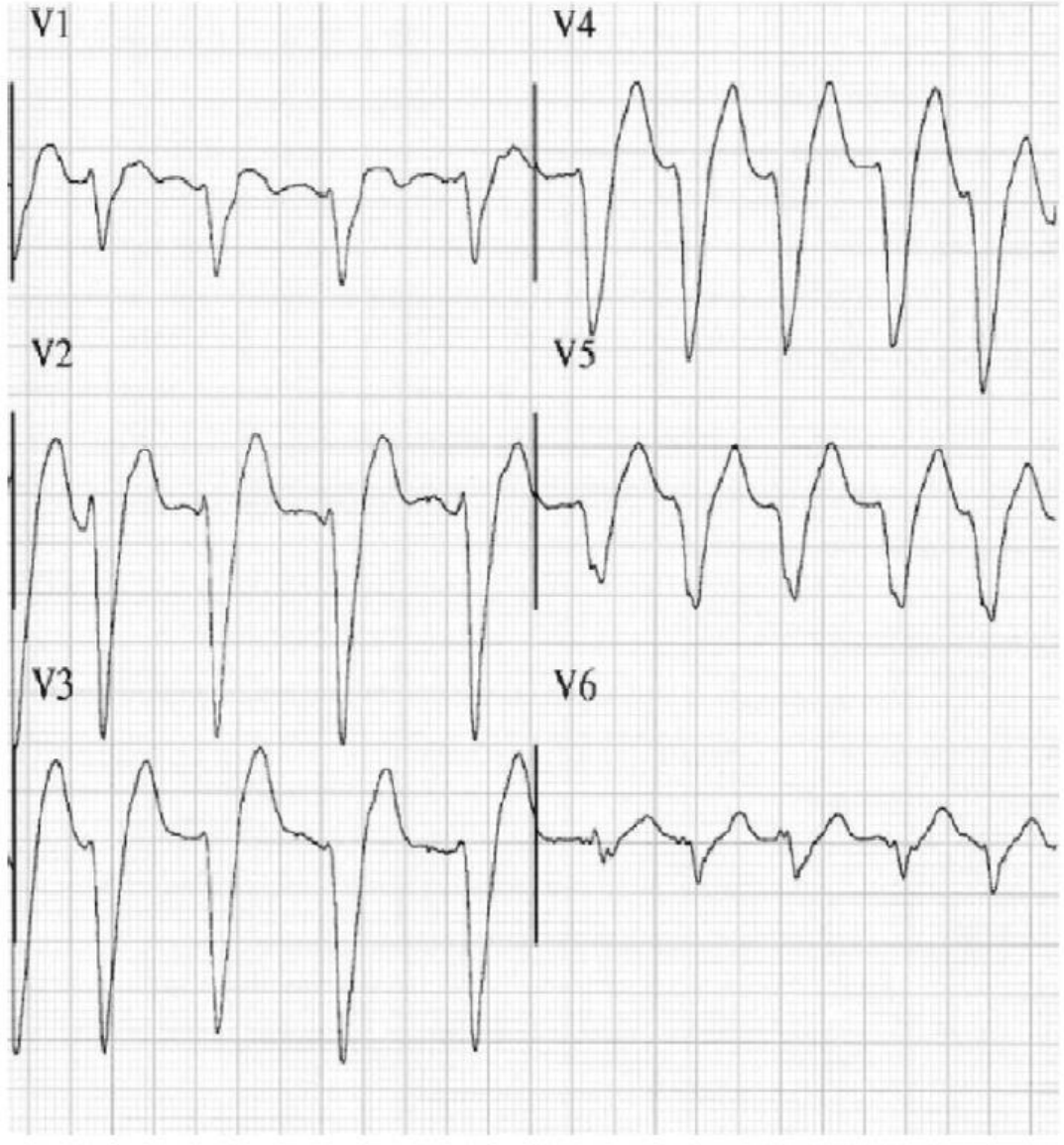
Fig. 2 Concentration–response curves for flecainide proarrhythmia in dogs with acute myocardial ischaemia (AMI) or chronic myocardial infarction (CMI) 72 h after coronary artery ligation (taken from Nattel) [60]

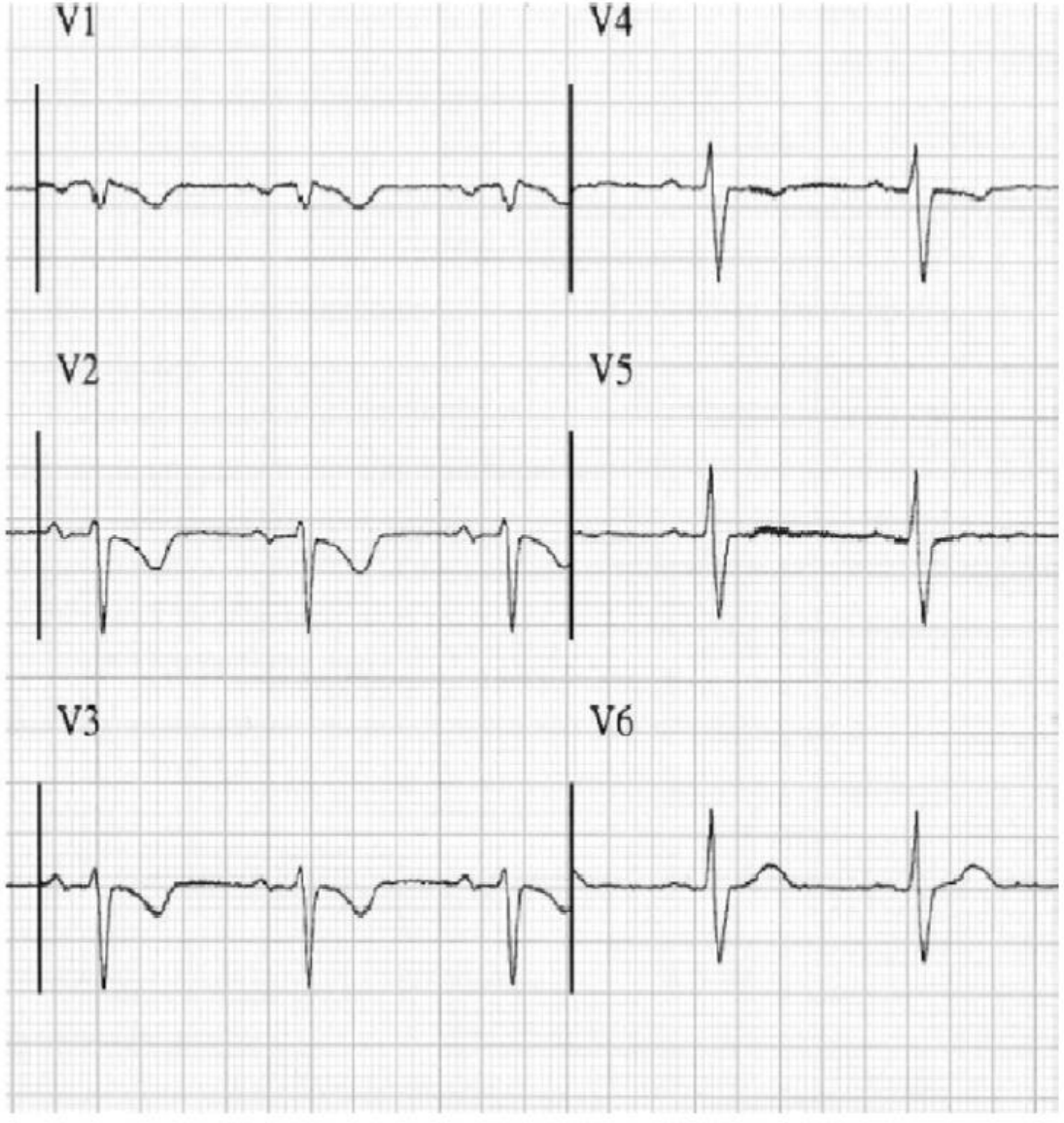
Table 3 Recommendations to minimise the proarrhythmic effects of flecainide

Recommendations
Keep strict adherence to prescribing guidelines
Avoid the use of flecainide in patients with structural heart disease
A better understanding of the pharmacology of the drugs prescribed
It will allow to identify possible drug interactions
Limit the number of drugs prescribed
Avoid the concomitant use of other antiarrhythmic drugs
Start the treatment at low doses that will be increased on the bases of patient's response and comorbidities
Increase dose after reaching steady-state levels (within 3–6 days)
Therapeutic drug monitoring (ECG, drug plasma levels) is recommended when making drug adjustments
Particularly in the elderly and in patients with hepatic and/or renal dysfunction
Monitor drug plasma levels to avoid toxic levels (>1000 ng/mL)
Check the efficiency and in particular the safety of the drug after the transition from an in-hospital to the ambulatory setting
Pill-in-the-pocket approach: only when flecainide has been previously proved safe in hospital and has a specific approval

ECG electrocardiogram

Flecainide induced bundle branch block





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ORIGINAL INVESTIGATIONS

Amiodarone, Anticoagulation, and Clinical Events in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

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ABSTRACT

BACKGROUND Amiodarone is an effective medication in preventing atrial fibrillation (AF), but it interferes with the metabolism of warfarin.

OBJECTIVES This study sought to examine the association of major thrombotic clinical events and bleeding with the use of amiodarone in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

METHODS Baseline characteristics of patients who received amiodarone at randomization were compared with those who did not receive amiodarone. The interaction between randomized treatment and amiodarone was tested using a Cox model, with main effects for randomized treatment and amiodarone and their interaction. Matching on the basis of a propensity score was used to compare patients who received and who did not receive amiodarone at the time of randomization.

RESULTS In ARISTOTLE, 2,051 (11.4%) patients received amiodarone at randomization. Patients on warfarin and amiodarone had time in the therapeutic range that was lower than patients not on amiodarone (56.5% vs. 63.0%; $p < 0.0001$). More amiodarone-treated patients had a stroke or a systemic embolism (1.58%/year vs. 1.19%/year; adjusted hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 1.03 to 2.10; $p = 0.0322$). Overall mortality and major bleeding rates were elevated, but were not significantly different in amiodarone-treated patients and patients not on amiodarone. When comparing apixaban with warfarin, patients who received amiodarone had a stroke or a systemic embolism rate of 1.24%/year versus 1.85%/year (HR: 0.68, 95% CI: 0.40 to 1.15), death of 4.15%/year versus 5.65%/year (HR: 0.74, 95% CI: 0.55 to 0.98), and major bleeding of 1.86%/year versus 3.06%/year (HR: 0.61, 95% CI: 0.39 to 0.96). In patients who did not receive amiodarone, the stroke or systemic embolism rate was 1.29%/year versus 1.57%/year (HR: 0.82, 95% CI: 0.68 to 1.00), death was 3.43%/year versus 3.68%/year (HR: 0.93, 95% CI: 0.83 to 1.05), and major bleeding was 2.18%/year versus 3.03%/year (HR: 0.72, 95% CI: 0.62 to 0.84). The interaction p values for amiodarone use by apixaban treatment effects were not significant.

CONCLUSIONS Amiodarone use was associated with significantly increased stroke and systemic embolism risk and a lower time in the therapeutic range when used with warfarin. Apixaban consistently reduced the rate of stroke and systemic embolism, death, and major bleeding compared with warfarin in amiodarone-treated patients and patients who were not on amiodarone. (J Am Coll Cardiol 2014;64:1541–50) © 2014 by the American College of Cardiology Foundation.

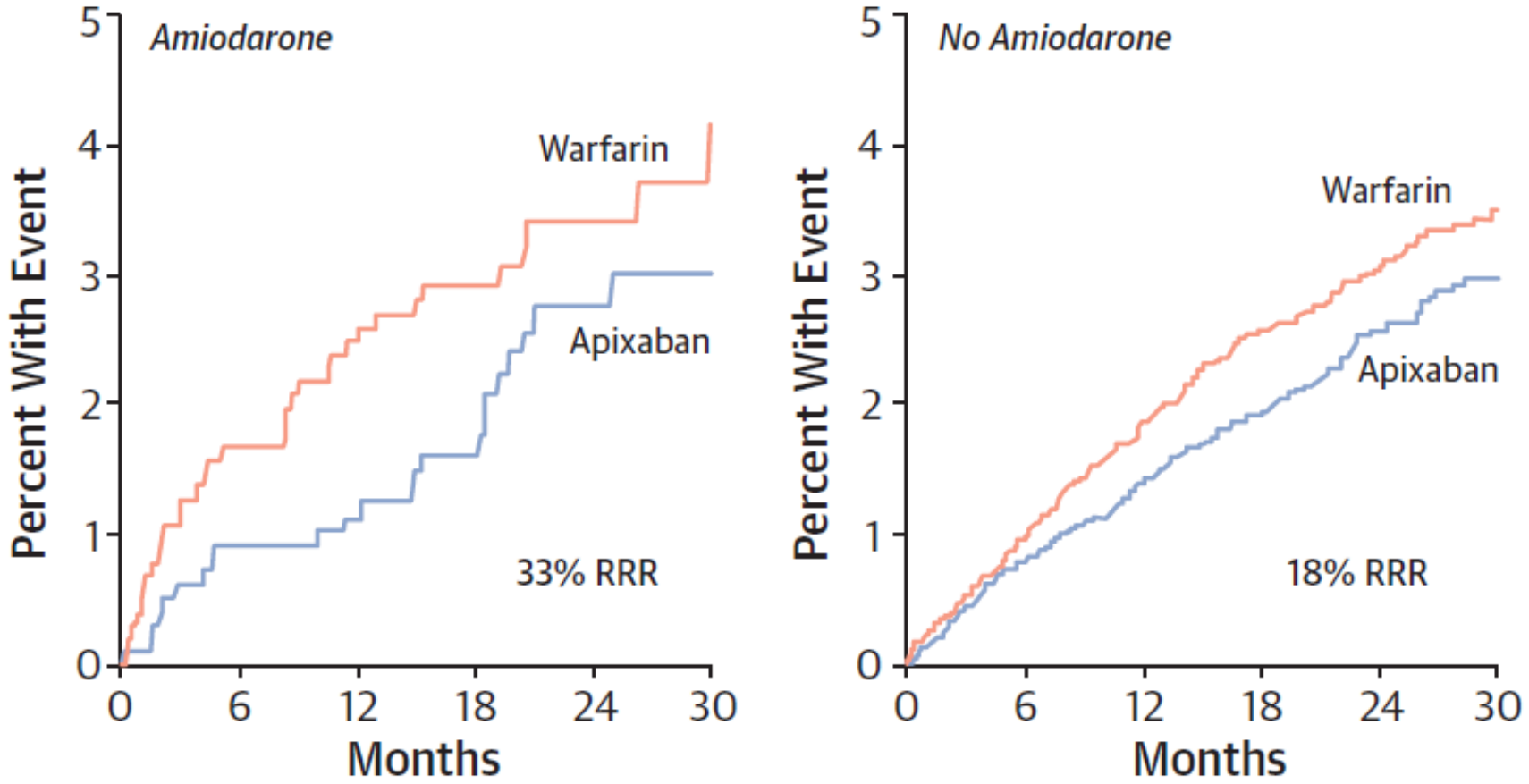


FIGURE 1 **Kaplan-Meier Curves of Stroke or Systemic Embolism**

Stroke or systemic embolism by amiodarone use at randomization in patients treated with apixaban or warfarin. RRR = relative risk ratio.

TABLE 2 Observed Rates and Number of Events for Efficacy and Safety Endpoints in Patients With Amiodarone and No Amiodarone at Randomization and by Study Drug Assignment

Event	Amiodarone				No Amiodarone				Interaction p Value
	Overall	Apixaban	Warfarin	HR (95% CI)*	Overall	Apixaban	Warfarin	HR (95% CI)*	
Efficacy endpoints									
Stroke or SE	1.55 (58)	1.24 (23)	1.85 (35)	0.68 (0.40–1.15)	1.43 (416)	1.29 (189)	1.57 (227)	0.82 (0.68–1.00)	0.4776
All-cause death	4.91 (187)	4.15 (78)	5.65 (109)	0.74 (0.55–0.98)	3.56 (1060)	3.43 (514)	3.68 (546)	0.93 (0.83–1.05)	0.1366
CV death	2.63 (100)	2.34 (44)	2.90 (56)	0.81 (0.54–1.20)	1.82 (541)	1.74 (260)	1.90 (281)	0.92 (0.77–1.09)	0.5611
Non-CV death	1.58 (60)	1.38 (26)	1.76 (34)	0.79 (0.47–1.31)	1.13 (335)	1.10 (165)	1.15 (170)	0.96 (0.78–1.19)	0.4728
MI	0.27 (10)	0.21 (4)	0.32 (6)	0.68 (0.19–2.41)	0.61(179)	0.58 (85)	0.65 (94)	0.90 (0.90–1.20)	0.6790
Safety endpoints									
Major bleeding	2.46 (82)	1.86 (31)	3.06 (51)	0.61 (0.39–0.96)	2.60 (690)	2.18 (293)	3.03 (397)	0.72 (0.62–0.84)	0.4894
Major/CRNM bleeding	5.12 (167)	3.92 (64)	6.31 (103)	0.63 (0.46–0.86)	4.99 (1298)	4.10 (542)	5.92 (756)	0.70 (0.62–0.78)	0.5226
Intracranial bleeding	0.74 (25)	0.30 (5)	1.19 (20)	0.25 (0.10–0.67)	0.54 (146)	0.35 (47)	0.74 (99)	0.46 (0.33–0.66)	0.2456

Values are %/year (n). *Hazard ratios are apixaban versus warfarin.

CI = confidence interval; CRNM = clinically relevant non-major; CV = cardiovascular; HR = hazard ratio; other abbreviations as in Table 1.

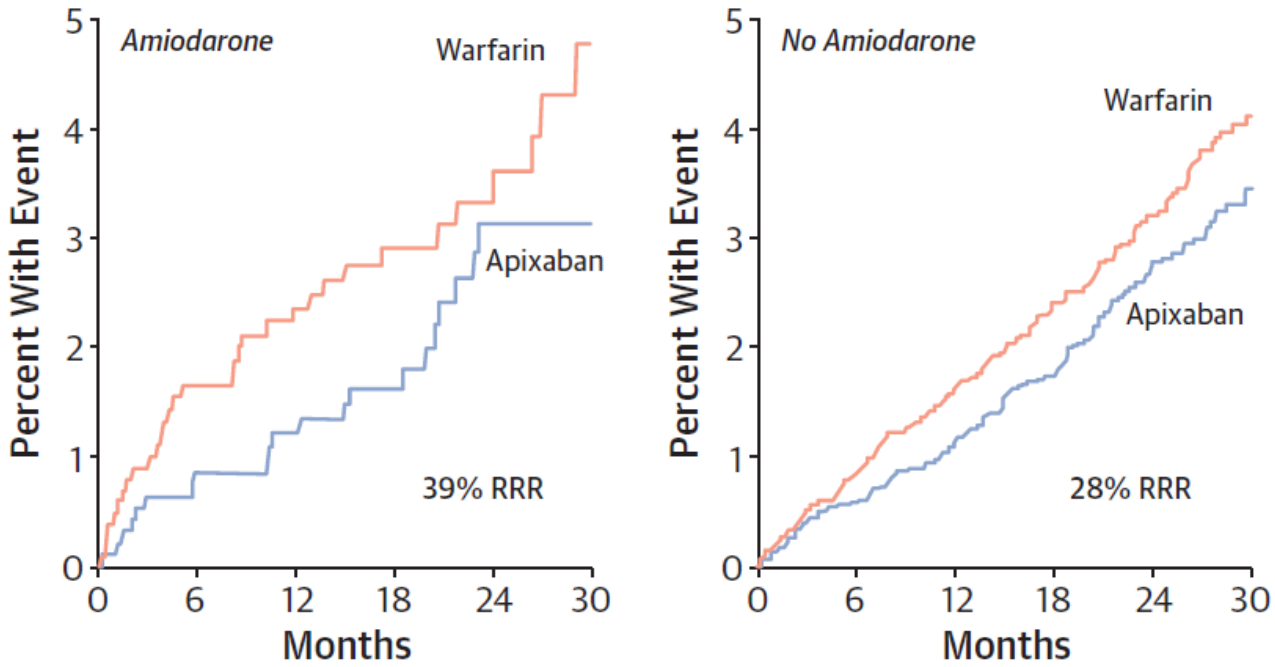
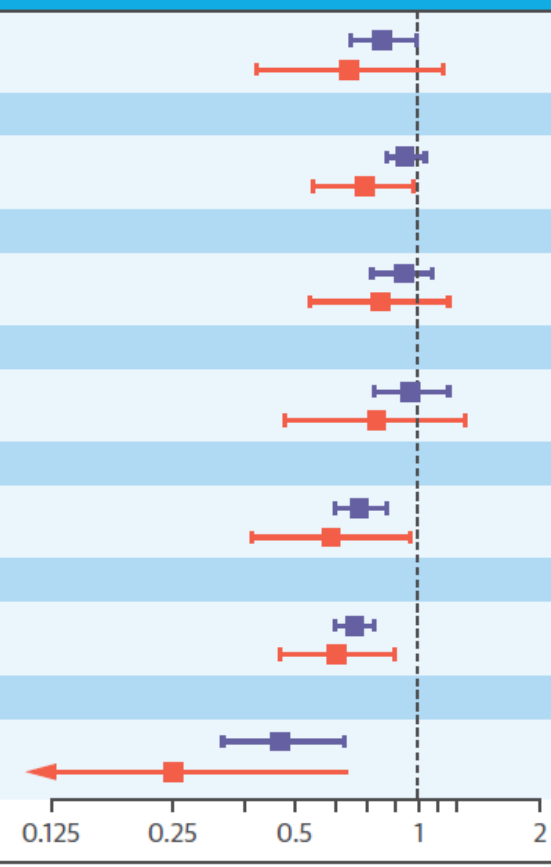


FIGURE 2 **Kaplan-Meier Curves of Major Bleeding**

International Society of Thrombosis and Hemostasis (ISTH) major bleeding by amiodarone use at randomization in patients treated with apixaban or warfarin. Abbreviation as in Figure 1.

Hazard Ratio

	EVENTS (RATE % PER YEAR) APIXABAN	WARFARIN	HR	INTERACTION P
Stroke or SE	1.29 (189) 1.24 (23)	1.57 (227) 1.85 (35)	0.82 (0.68 - 1.00) 0.68 (0.40 - 1.15)	0.48
Death	3.43 (514) 4.15 (78)	3.68 (546) 5.65 (109)	0.93 (0.83 - 1.05) 0.74 (0.55 - 0.98)	0.14
CV Death	1.74 (260) 2.34 (44)	1.90 (281) 2.90 (56)	0.92 (0.77 - 1.09) 0.81 (0.54 - 1.20)	0.56
Non-CV Death	1.10 (165) 1.38 (26)	1.15 (170) 1.76 (34)	0.96 (0.78 - 1.19) 0.79 (0.47 - 1.31)	0.47
Major Bleeding	2.18 (293) 1.86 (31)	3.03 (397) 3.06 (51)	0.72 (0.62 - 0.84) 0.61 (0.39 - 0.96)	0.49
Major/ Clinically Relevant Non-major Bleeding	4.10 (542) 3.92 (64)	5.92 (756) 6.31 (103)	0.70 (0.62 - 0.78) 0.63 (0.46 - 0.87)	0.52
Intracranial Bleeding	0.35 (47) 0.30 (5)	0.74 (99) 1.19 (20)	0.46 (0.33 - 0.66) 0.25 (0.10 - 0.67)	0.25



CENTRAL ILLUSTRATION **Patient Outcomes by Amiodarone Use at Randomization**

Event rates and hazard ratios (HRs) comparing apixaban to warfarin by amiodarone use at randomization. CV = cardiovascular; SE = systemic embolism.

Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: Results from the ROCKET AF trial

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BACKGROUND Antiarrhythmic drugs (AADs) and anticoagulation are mainstays of atrial fibrillation (AF) treatment.

OBJECTIVE To study the use and outcomes of AAD therapy in anticoagulated patients with AF.

METHODS Patients in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial (N = 14,264) were stratified by AAD use at baseline: amiodarone, other AAD, or no AAD. Multivariable adjustment was performed to compare stroke, bleeding, and death across AAD groups as well as across treatment assignment (rivaroxaban or warfarin).

RESULTS Of 14,264 patients randomized, 1681 (11.8%) were treated with an AAD (1144 [8%] with amiodarone and 537 [3.8%] with other AADs). Amiodarone-treated patients were less often female (38% vs 48%), had more persistent AF (64% vs 40%), and more concomitant heart failure (71% vs 41%) than were patients receiving other AADs. Patients receiving no AAD more closely resembled amiodarone-treated patients. Time in therapeutic range was significantly lower in warfarin-treated patients receiving amiodarone than in those receiving no AAD (50% vs 58%; $P < .0001$). Compared with no AAD, neither amiodarone (adjusted hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.74–1.31; $P = .9$) nor other AADs (adjusted HR 0.66; 95% CI 0.37–1.17; $P = .15$) were associated with increased mortality. Similar results were observed for embolic and bleeding outcomes. Treatment effects of rivaroxaban vs warfarin in patients receiving no AAD were consistent with results from the overall trial (primary end point: adjusted HR 0.82; 95% CI 0.68–0.98; $P_{interaction} = .06$; safety end point: adjusted HR 1.12; 95% CI 0.90–1.24; $P_{interaction} = .33$).

CONCLUSION Treatment with AADs was not associated with increased morbidity or mortality in anticoagulated patients with AF. The effect of amiodarone on outcomes in patients receiving rivaroxaban requires further investigation.

KEYWORDS Atrial fibrillation; Antiarrhythmic drugs; Rivaroxaban; Warfarin; Outcomes

ABBREVIATIONS **AAD** = antiarrhythmic drug; **AF** = atrial fibrillation; **CI** = confidence interval; **CNS** = central nervous system; **ED** = emergency department; **GI** = gastrointestinal; **HR** = hazard ratio; **INR** = international normalized ratio; **MI** = myocardial infarction; **NMCR** = nonmajor clinically relevant; **ROCKET AF** = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; **TTR** = time in therapeutic range; **VKA** = vitamin K antagonist

(Heart Rhythm 2014;11:925–932)

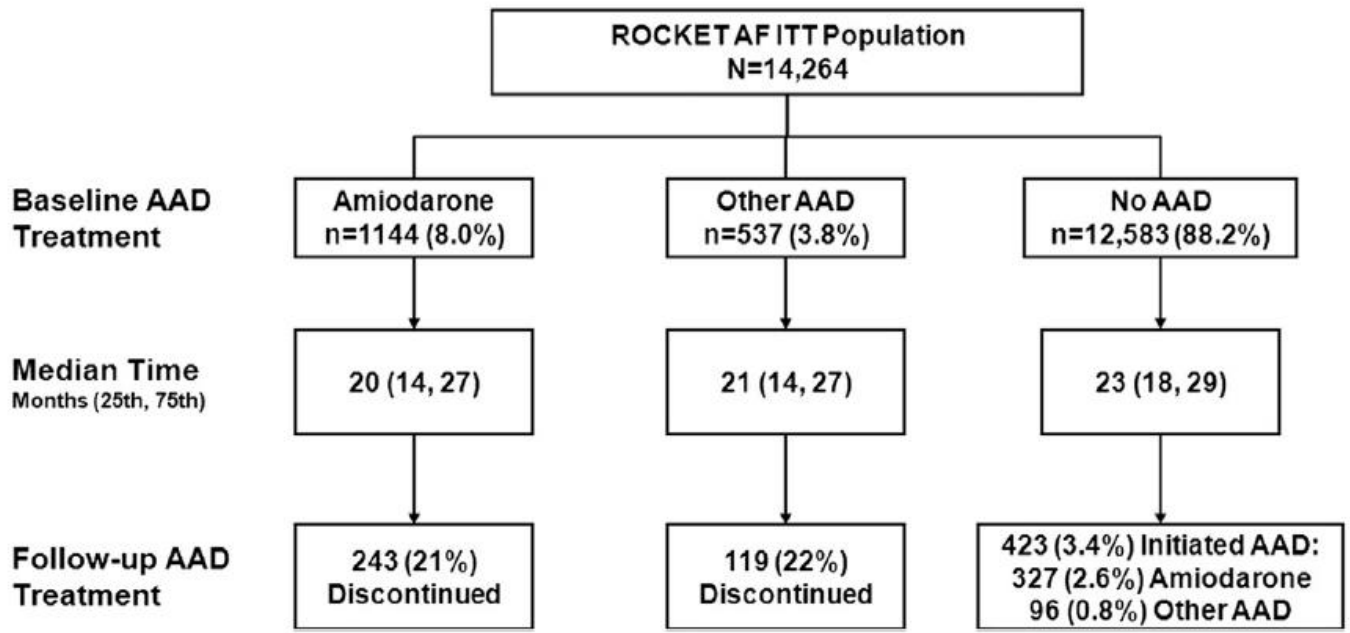


Figure 1 Derivation of study population and persistence of AAD therapies. Patients were stratified by AAD use at baseline: amiodarone, other AAD, or no AAD. AAD = antiarrhythmic drug; ITT = intention to treat; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

Table 1 Baseline characteristics

Characteristic	Amiodarone (n = 1144)	Other AAD (n = 537)	No AAD (n = 12,583)
Treatment assignment			
Rivaroxaban	572 (50.0)	285 (53.1)	6274 (49.9)
Warfarin	572 (50.0)	252 (46.9)	6309 (50.1)
Age (y)	70 (61, 77)	70 (63, 76)	73 (66, 78)
Sex: female	439 (38.4)	255 (47.5)	4966 (39.5)
Atrial fibrillation			
New onset	21 (1.8)	1 (0.2)	180 (1.4)
Paroxysmal	393 (34.4)	319 (59.4)	1802 (14.3)
Persistent	730 (63.8)	217 (40.4)	10,601 (84.2)
$CHADS_2$ score	3.5 ± 0.9	3.3 ± 0.9	3.5 ± 0.9
$CHADS_2$ score			
1	0	0	3 (<0.1)
2	120 (10.5)	89 (16.6)	1650 (13.1)
3	488 (42.7)	254 (47.3)	5474 (43.5)
4	370 (32.3)	139 (25.9)	3582 (28.5)
5	148 (12.9)	47 (8.8)	1618 (12.9)
6	18 (1.6)	8 (1.5)	256 (2.0)
Presenting characteristics			
BMI (kg/m^2)	28.9 (25.7, 32.7)	28.1 (25.0, 31.6)	28.1 (25.1, 31.9)
Systolic BP (mm Hg)	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic BP (mm Hg)	80 (72, 86)	80 (70, 84)	80 (70, 85)
Heart rate (beats/min)	75 (65, 86)	70 (62, 80)	76 (68, 86)
Creatinine clearance* (mL/min)	67 (52, 87)	74 (57, 98)	67 (52, 86)
Baseline comorbidities			
Prior ablation for AF	32 (2.8)	31 (5.8)	258 (2.1)
Prior stroke, TIA, or non-CNS embolism	643 (56.2)	363 (67.6)	6805 (54.1)
PAD	68 (5.9)	18 (3.4)	753 (6.0)
Hypertension	1063 (92.9)	463 (86.2)	11,384 (90.5)
Diabetes	457 (39.9)	182 (33.9)	5056 (40.2)
Prior MI	193 (16.9)	59 (11.0)	2216 (17.6)
CHF	813 (71.1)	222 (41.3)	7873 (62.6)
COPD	122 (10.7)	45 (8.4)	1330 (10.6)
Medications			
Prior VKA use	601 (52.5)	346 (64.4)	7957 (63.2)
Prior chronic ASA use	486 (42.5)	176 (32.8)	4543 (36.1)
ACE-I/ARB at baseline	880 (76.9)	356 (66.3)	9347 (74.3)
β-Blocker at baseline	574 (50.2)	422 (78.6)	8254 (65.6)
Digitalis at baseline	274 (24.0)	82 (15.3)	5112 (40.6)
Diuretic at baseline	694 (60.7)	225 (41.9)	7571 (60.2)

Data are presented as median (25th, 75th percentile), mean ± SD, or n (%).

AAD = antiarrhythmic drug; ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ASA = aspirin; BMI = body mass index; BP = blood pressure; CHF = congestive heart failure; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PAD = peripheral arterial disease; TIA = transient ischemic attack; VKA = vitamin K antagonist.

*Creatinine clearance calculated by using the Cockcroft-Gault equation.

Table 2 Anticoagulation control by the AAD group among warfarin-treated patients

	Amiodarone (n = 558)	Other AAD (n = 246)	No AAD (n = 6221)
TTR, INR 2–3	50 (33, 64)	61 (45, 74)	58 (43, 71)
Time INR <2	27 (16, 45)	21 (11, 37)	24 (13, 39)
Time INR 1.5–<2	20 (12, 29)	15 (8, 24)	18 (11, 28)
Time INR 1–<1.5	4 (0, 13)	2 (0, 9)	3 (0, 9)
Time INR <1	0 (0, 0)	0 (0, 0)	0 (0, 0)
Time INR >3	16 (9, 26)	13 (5, 21)	13 (7, 21)
Time INR >3–4	12 (6, 19)	11 (5, 17)	11 (5, 17)
Time INR >4–5	2 (0, 4)	0 (0, 2)	1 (0, 3)
Time INR >5 (%)	0 (0, 1)	0 (0, 0)	0 (0, 0)

Data are presented as median percent time (25th, 75th percentile). *P* values for TTR: amiodarone vs no AAD, <.0001; other AAD vs no AAD, .16; and amiodarone vs other AAD, <.0001 (calculated by using pairwise Wilcoxon rank sum tests). A total of 5% of the patients had at least 1 INR value <1; among these patients, the median amount of time spent in this range was 1.1%. A total of 29% of the patients had at least 1 INR value >5; among these patients, the median amount of time spent in this range was 1.6%.

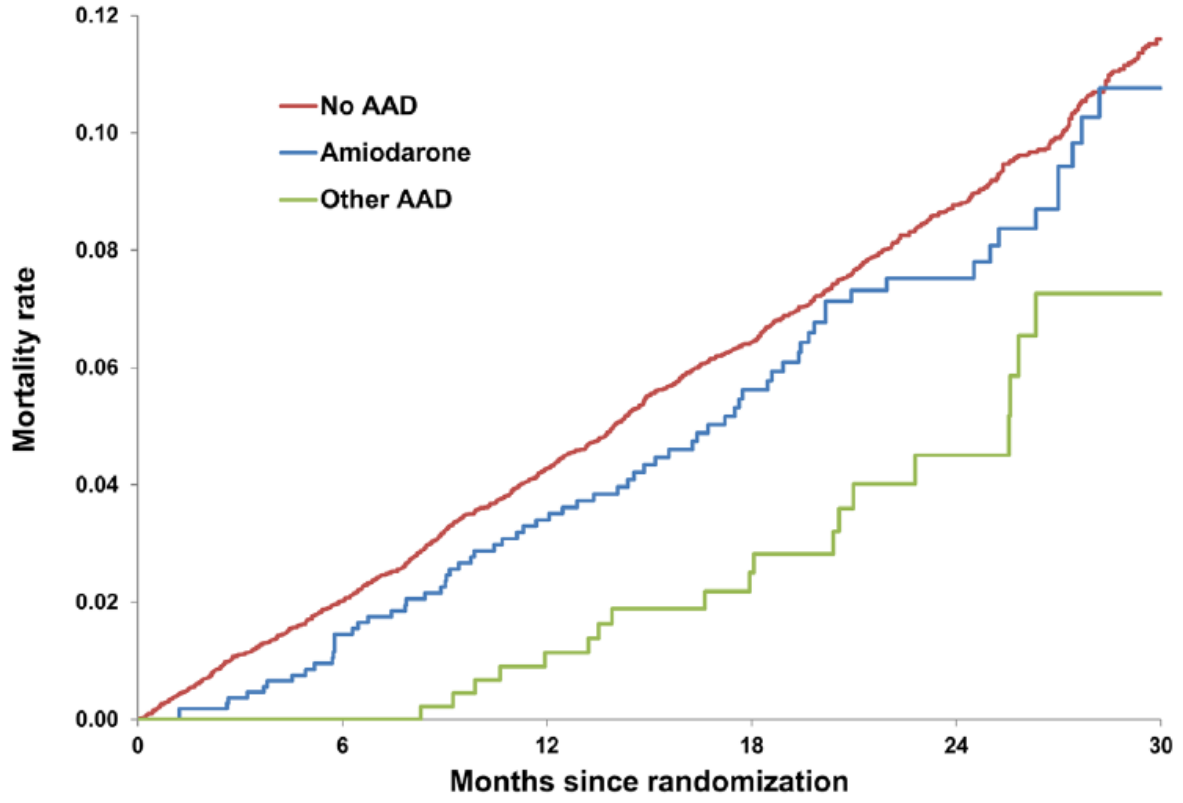
AAD = antiarrhythmic drug; INR = international normalized ratio; TTR = time in therapeutic range.

Table 3 Adjusted outcomes stratified by AAD use at baseline

	Amiodarone vs no AAD		Other AAD vs no AAD		Amiodarone vs other AAD	
Outcome	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Efficacy outcomes						
All-cause death	0.98 (0.74–1.31)	.90	0.66 (0.37–1.17)	.15	1.49 (0.78–2.84)	.22
Vascular death	0.89 (0.61–1.31)	.56	0.60 (0.27–1.34)	.21	1.48 (0.61–3.61)	.39
Non–vascular death	1.14 (0.76–1.71)	.52	0.74 (0.32–1.70)	.48	1.54 (0.62–3.81)	.35
Stroke or non-CNS embolism	1.17 (0.76–1.81)	.48	0.57 (0.26–1.22)	.15	2.06 (0.87–4.90)	.10
Stroke, non-CNS embolism, MI, or vascular death	1.06 (0.80–1.39)	.69	0.79 (0.49–1.26)	.32	1.34 (0.78–2.32)	.29
Stroke	1.03 (0.67–1.57)	.90	0.59 (0.26–1.31)	.20	1.75 (0.73–4.21)	.21
Non-CNS embolism	2.34 (0.83–6.59)	.11	0.56 (0.08–3.90)	.55	4.21 (0.54–32.5)	.17
MI	1.76 (1.11–2.77)	**.02**	1.35 (0.63–2.92)	.44	1.30 (0.53–3.17)	.56
Cardiac failure	1.17 (0.95–1.44)	.14	0.86 (0.52–1.43)	.56	1.36 (0.79–2.35)	.27
Hospitalization	1.13 (0.92–1.39)	.25	1.06 (0.79–1.41)	.70	1.06 (0.75–1.49)	.75
ED visit	0.91 (0.78–1.07)	.26	1.21 (0.96–1.51)	.10	0.76 (0.58–1.00)	.99
Safety outcomes						
Major or NMCR bleeding	0.98 (0.81–1.18)	.81	0.83 (0.63–1.09)	.18	1.18 (0.85–1.64)	.32
Major bleeding	0.90 (0.61–1.31)	.58	0.77 (0.45–1.32)	.34	1.17 (0.61–2.23)	.64
NMCR bleeding	0.99 (0.80–1.21)	.90	0.80 (0.59–1.09)	.16	1.23 (0.86–1.77)	.25

AAD = antiarrhythmic drug; CI = confidence interval; CNS = central nervous system; ED = emergency department; HR = hazard ratio; MI = myocardial infarction; NMCR = nonmajor clinically relevant.

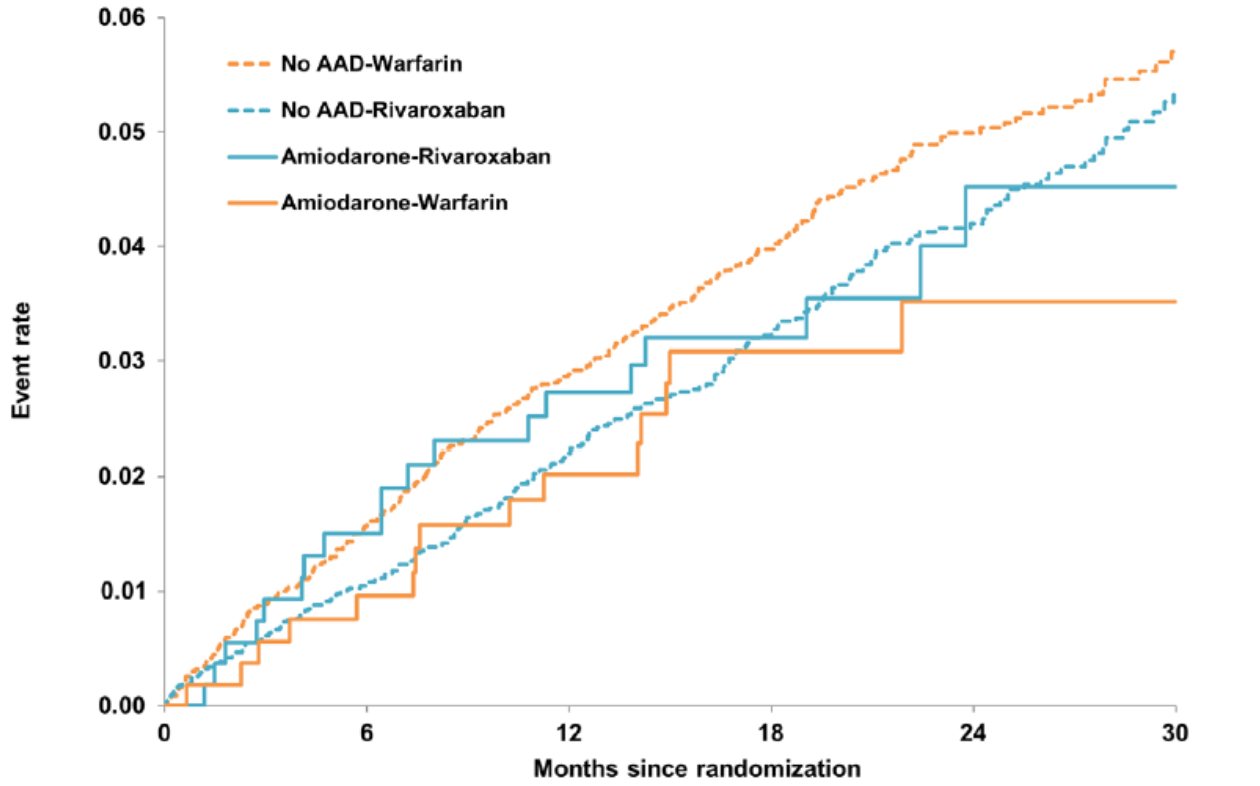
All-Cause Mortality



No AAD	12503	11865	11247	8201	4974	2132
Amiodarone	1132	991	904	624	359	118
Other AAD	536	464	422	305	169	69

Figure 2 Kaplan-Meier curves for all-cause mortality stratified by AAD use at baseline. P = NS for all 3 pairwise comparisons by using multivariable Cox models. AAD = antiarrhythmic drug.

Stroke or non-CNS embolization



No AAD-Warfarin	6273	5886	5531	4022	2432	1041
No AAD-Rivaroxaban	6230	5879	5546	4009	2412	1024
Amiodarone-Rivaroxaban	567	499	456	308	178	56
Amiodarone-Warfarin	565	485	437	305	171	57

Figure 3 Kaplan-Meier curves for stroke or non-CNS embolism in patients randomized to rivaroxaban vs warfarin, which were stratified by amiodarone use at baseline (vs no AAD). AAD = antiarrhythmic drug; CNS = central nervous system.

Table 4 Adjusted outcomes of rivaroxaban vs warfarin stratified by amiodarone use at baseline

	Amiodarone			No AAD			
Outcome	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Interaction *P* (amiodarone and treatment)
Stroke or non-CNS embolism	2.14 (19)	1.74 (15)	1.71 (0.80–3.65)	2.16 (237)	2.54 (279)	**0.82 (0.68–0.98)**	.063
Bleeding							
Major or NMCR bleeding	15.90 (108)	13.82 (92)	1.35 (0.94–1.92)	15.00 (1284)	14.53 (1261)	**1.12 (1.00–1.25)**	.33
Major bleeding	3.84 (29)	1.88 (14)	2.20 (0.98–4.91)	3.61 (343)	3.58 (347)	1.05 (0.90–1.24)	.078
ICH	0.52 (4)	0.27 (2)	2.42 (0.37–16.0)	0.50 (48)	0.78 (77)	**0.61 (0.42–0.88)**	.16
GI	1.70 (13)	0.40 (3)	4.58 (0.92–22.8)	1.75 (168)	1.14 (112)	**1.68 (1.30–2.18)**	.23
Fatal	0.13 (1)	0.40 (3)	0.48 (0.06–3.83)	0.25 (24)	0.50 (49)	**0.49 (0.30–0.80)**	.98
NMCR bleeding	12.28 (85)	12.03 (81)	1.24 (0.84–1.83)	11.92 (1035)	11.28 (993)	**1.15 (1.01–1.31)**	.71

AAD = antiarrhythmic drug; CI = confidence interval; CNS = central nervous system; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; NMCR = nonmajor clinically relevant.

Left Ventricular Hypertrophy and Antiarrhythmic Drugs in Atrial Fibrillation: Impact on Mortality

ROY CHUNG, M.D., PENNY L. HOUGHTALING, M.S., MICHAEL TCHOU, M.D., MARK J. NIEBAUER, M.D., PH.D., BRUCE D. LINDSAY, M.D., PATRICK J. TCHOU, M.D., and MINA K. CHUNG, M.D.

From the Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio

Background: *Despite sparse clinical data, current atrial fibrillation (AF) guidelines favor amiodarone as a drug of choice for patients with left ventricular hypertrophy (LVH).*

Objective: *This study tested the hypothesis that patients with persistent AF and LVH on nonamiodarone antiarrhythmics have higher mortality compared to patients on amiodarone.*

Methods: *In an observational cohort analysis of patients who underwent cardioversion for AF, patients with LVH, defined as left ventricular wall thickness ≥1.4 cm, by echocardiogram prior to their first cardioversion, were included; clinical data, including antiarrhythmic drugs and ejection fraction (LVEF), were collected. Mortality, determined via the Social Security Death Index, was analyzed using Kaplan-Meier and Cox proportional hazards models to determine whether antiarrhythmic drugs were associated with higher mortality.*

Results: *In 3,926 patients, echocardiographic wall thickness was available in 1,399 (age 66.8 ± 11.8 years, 67% male, LVEF 46 ± 15%, septum 1.3 ± 0.4, posterior wall 1.2 ± 0.2 cm), and 537 (38%) had LVH ≥1.4 cm. Among 537 patients with LVH, mean age was 67.5 ± 11.7 years, 76.4% were males, and mean LVEF was 48.3 ± 13.3%. Amiodarone was associated with lower survival (log rank P = 0.001), including after adjusting for age, LVEF, and coronary artery disease (P = 0.023). In propensity-score matched cohorts with LVH treated with no drugs, nonamiodarone antiarrhythmic drugs (non-AADs), or amiodarone (N = 65 each group), there was early lower survival in patients on amiodarone (P = 0.05).*

Conclusions: *Patients with persistent AF and LVH on non-AADs do not have higher mortality compared to patients on amiodarone. Importantly, these findings do not support amiodarone as a superior choice in patients with LVH. (PACE 2014; 37:1338–1348)*

Table I.

Baseline Characteristics in the Total Cohort, by Antiarrhythmic Drug Use, and by Presence or Absence of LVH (≥1.4 cm Wall Thickness)

		LVH ≥ 1.4 cm			Antiarrhythmic Drug Groups			
	Total, N = 1,399	No N = 862	Yes N = 537	p Value	No AAD N = 730	Nonamiodarone AAD N = 367	Amiodarone N = 302	p Value
Age (years)	66.8 ± 11.8	66.3 ± 11.8	67.5 ± 11.7	0.070	66.8 ± 11.5	64.8 ± 12.1	67 ± 11.8	0.001
Sex, male, N	975 (69.7%)	565 (65.5%)	410 (76.4%)	0.001	521 (71.4%)	230 (62.7%)	224 (74.2%)	0.002
Race				0.466				0.104
Caucasian	1279 (92.5%)	796 (93.2%)	483 (91.5%)		654 (90.8%)	342 (94.5%)	283 (94.3%)	
African American	97 (7.0%)	55 (6.4%)	42 (8%)		61 (8.5%)	19 (5.2%)	17 (5.7%)	
Other	6 (0.4%)	3 (0.4%)	3 (0.6%)		5 (0.7%)	1 (0.3%)	0 (0%)	
Cardiovascular diagnoses								
No structural heart disease	228 (16.3%)	154 (17.9%)	74 (13.8%)	0.044	134 (18.4%)	77 (21.0%)	17 (5.6%)	0.001
Coronary artery disease	475 (34%)	286 (33.2%)	189 (35.2%)	0.439	241 (33.0%)	95 (25.9%)	139 (46.0%)	0.001
Valvular heart disease	456 (32.6%)	275 (31.9%)	181 (33.7%)	0.484	189 (25.9%)	149 (40.6%)	118 (39.1%)	0.001
Primary cardiomyopathy	110 (7.9%)	79 (9.2%)	31 (5.8%)	0.062	48 (6.6%)	16 (4.4%)	46 (15.2%)	0.001
Congenital heart disease	23 (1.6%)	14 (1.6%)	9 (1.7%)	0.941	8 (1.1%)	10 (2.7%)	5 (1.7%)	0.135
Hypertrophic cardiomyopathy	35 (2.5%)	7 (0.8%)	28 (5.2%)	0.001	13 (1.8%)	14 (3.8%)	8 (2.6%)	0.124
LVEF (%)	46.1 ± 14.6%	44.8 ± 15.1	48.3 ± 13.3	0.001	47.1 ± 14.1	51.8 ± 10	37.0 ± 16.0	0.001
Smoker	713 (56.4%)	428 (55.3%)	285 (58.3%)	0.317	355 (54.0%)	176 (52.9%)	182 (66.4%)	0.001
Echocardiographic data								
LA size (cm)	4.71 ± 0.83	4.64 ± 0.82	4.82 ± 0.82	0.001	4.66 ± 0.81	4.67 ± 0.83	4.88 ± 0.83	0.001
LV systolic diameter (cm)	3.60 ± 1.14	3.72 ± 1.19	3.41 ± 1.02	0.001	3.50 ± 1.08	3.26 ± 0.85	4.25 ± 1.32	0.001
LV diastolic diameter (cm)	5.14 ± 0.98	5.26 ± 0.98	4.96 ± 0.94	0.001	5.07 ± 0.93	4.89 ± 0.83	5.63 ± 1.08	0.001
AAD use								
Disopyramide	13 (0.9%)	9 (1.0%)	4 (0.7%)	0.571	0	13 (3.5%)	0	
Procainamide	64 (4.7%)	40 (4.6%)	26 (4.8%)	0.863	0	64 (17.4%)	0	
Quinidine	13 (0.9%)	8 (0.9%)	5 (0.9%)	0.995	0	11 (3.0%)	0	
Flecainide	101 (7.2%)	64 (7.4%)	37 (6.9%)	0.707	0	100 (27.2%)	0	
Propafenone	37 (2.6%)	24 (2.8%)	13 (2.4%)	0.680	0	37 (10.1%)	0	
Moricizine	3 (0.2%)	2 (0.2%)	1 (0.2%)	0.857	0	3 (0.7%)	0	
Dofetilide	14 (1.0%)	12 (1.4%)	2 (0.4%)	0.062	0	14 (0.8%)	0	
Sotalol	131 (9.4%)	80 (9.3%)	51 (9.5%)	0.892	0	131 (35.7%)	0	
Amiodarone	302 (21.6%)	187 (21.7%)	115 (21.4%)	0.902	0	0	302 (100%)	

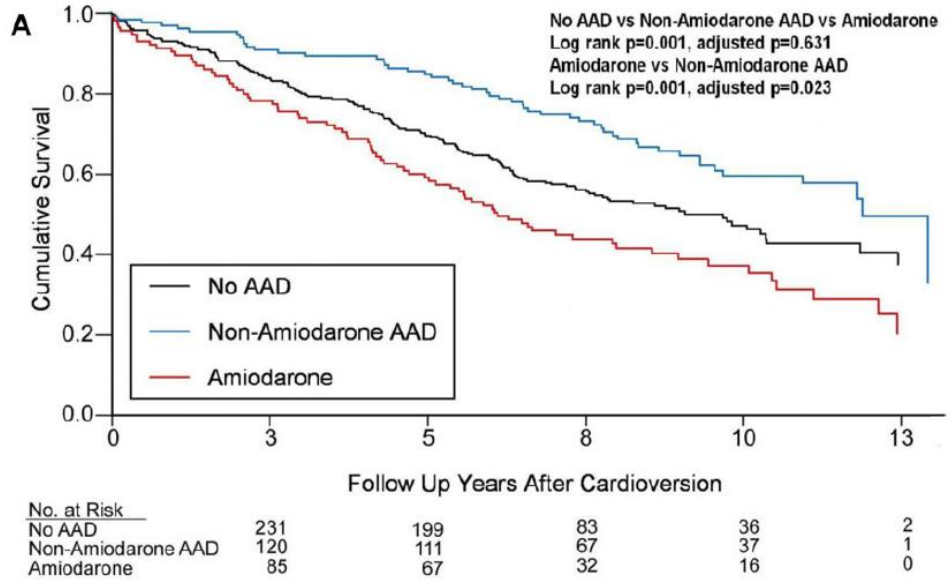
AAD = antiarrhythmic drug; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy.

Table II.

Baseline Characteristics of Patients with and Without LVH (≥1.4 cm), Stratified by Antiarrhythmic Drug Use

	No LVH (N = 862)				LVH ≥ 1.4 cm (N = 537)			
	No AAD N = 422 (49.0%)	Nonamiodarone AAD N = 233 (27.0%)	Amiodarone N = 187 (21.7%)	p Value	No AAD N = 288 (53.6%)	Nonamiodarone AAD N = 134 (25.0%)	Amiodarone N = 115 (21.4%)	p Value
Age (years)	67.1 ± 11.6	65.4 ± 12.0	66.0 ± 12.0	0.189	68.8 ± 11.2	63.7 ± 12.5	68.8 ± 11.0	0.001
Sex, male	297 (67.2%)	133 (57.1%)	135 (72.2%)	0.003	224 (77.8%)	97 (72.4%)	89 (77.4%)	0.459
Race				0.390				0.252
Caucasian	403 (92.0%)	218 (94.8%)	175 (94.1%)		251 (89.0%)	124 (93.9%)	108 (94.7%)	
African American	32 (7.3%)	12 (5.2%)	11 (5.9%)		29 (10.3%)	7 (5.3%)	6 (5.3%)	
Other	3 (0.7%)	0 (0%)	0 (0%)		2 (0.7%)	1 (0.8%)	0 (0%)	
Cardiovascular diagnoses								
No structural heart disease	91 (20.6%)	53 (22.7%)	10 (5.3%)	0.001	43 (18.4%)	24 (21.0%)	7 (5.6%)	0.019
Coronary artery disease	138 (31.2%)	64 (27.5%)	84 (44.9%)	0.001	103 (35.8%)	31 (23.1%)	55 (47.8%)	0.001
Valvular heart disease	113 (25.6%)	92 (39.5%)	70 (37.4%)	0.001	76 (26.4%)	57 (42.5%)	48 (31.7%)	0.001
Primary cardiomyopathy	34 (7.7%)	12 (5.2%)	33 (17.6%)	0.001	14 (4.9%)	4 (3.0%)	13 (11.3%)	0.012
Congenital heart disease	4 (0.9%)	5 (2.1%)	5 (2.7%)	0.21	4 (1.4%)	5 (3.7%)	0 (0%)	0.063
Hypertrophic cardiomyopathy	4 (0.9%)	1 (0.4%)	2 (1.1%)	0.731	9 (3.1%)	13 (9.7%)	6 (5.2%)	0.018
LVEF (%)	46.0 ± 14.7	50.9 ± 10.2	34.5 ± 16.1	0.001	48.9 ± 12.9	53.3 ± 9.4	40.9 ± 15.0	0.001
Smoker	207 (52.9%)	109 (51.7%)	112 (65.1%)	0.013	148 (55.6%)	67 (54.9%)	70 (68.6%)	0.055
Echocardiographic data								
LA size (cm)	4.60 ± 0.83	4.56 ± 0.80	4.85 ± 0.82	0.001	4.76 ± 0.78	4.88 ± 0.86	4.92 ± 0.87	0.175
LV systolic diameter (cm)	3.64 ± 1.13	3.30 ± 0.85	4.44 ± 1.38	0.001	3.30 ± 0.97	3.18 ± 0.84	3.94 ± 1.17	0.001
LV diastolic diameter (cm)	5.20 ± 0.95	4.94 ± 0.80	5.80 ± 1.07	0.001	4.86 ± 0.86	4.80 ± 0.87	5.36 ± 1.06	0.001
AAD use								
Disopyramide	0	9 (3.9%)	0		0	4 (3.0%)	0	
Procainamide	0	40 (17.2%)	0		0	24 (17.9%)	0	
Quinidine	0	7 (3.0%)	0		0	4 (3.0%)	0	
Flecainide	0	63 (27%)	0		0	37 (27.6%)	0	
Propafenone	0	24 (10.3%)	0		0	13 (9.7%)	0	
Moricizine	0	2 (0.9%)	0		0	1 (0.7%)	0	
Dofetilide	0	12 (5.2%)	0		0	2 (1.5%)	0	
Sotalol	0	80 (34.3%)	0		0	51 (38.1%)	0	
Amiodarone	0	0	187 (100%)		0	0	115 (100%)	

AAD = antiarrhythmic drug; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy.



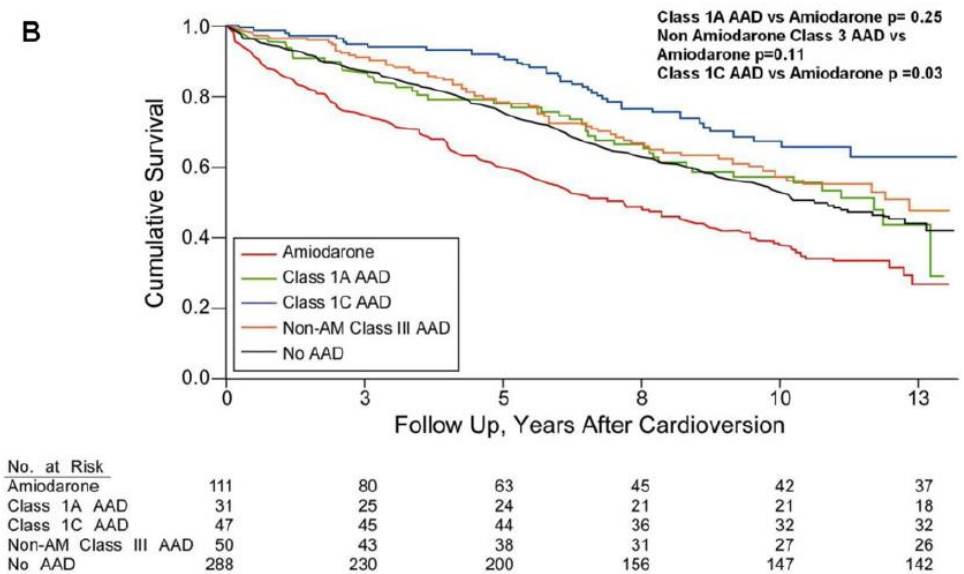


Figure 1. *Kaplan-Meier survival analysis stratified by antiarrhythmic drug (AAD) use in patients with left ventricular hypertrophy (≥1.4 cm septal or posterior wall thickness). (A) Analysis in patients stratified by no antiarrhythmic drug, amiodarone, and nonamiodarone antiarrhythmic drug use. (B) Analysis in patients stratified by no AAD, class IA, class 1C, amiodarone, and nonamiodarone class III (non-AM class III) AAD use.*

Table III.

Predictors of Mortality in Patients with LVH on AADs by Cox Proportional Hazards Modeling

Variable	Hazard Ratio	95% Confidence Interval	p Value
Age, yr	1.051	1.030, 1.072	0.001
LVEF, %	0.982	0.968, 0.996	0.010
CAD	0.973	0.652, 1.451	0.893
Smoker	1.647	1.097, 2.494	0.016
Amiodarone	1.655	1.072, 2.555	0.023

N = 249. AAD = antiarrhythmic drug; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy.

Amiodarone induced QT prolongation 54/M

Jeong, Yeonbeom ID:0870201 09-JAN-2015 11:33:28 Kosin University Hospital

54 yr
Male Asian
0kg
Room:
Loc:13

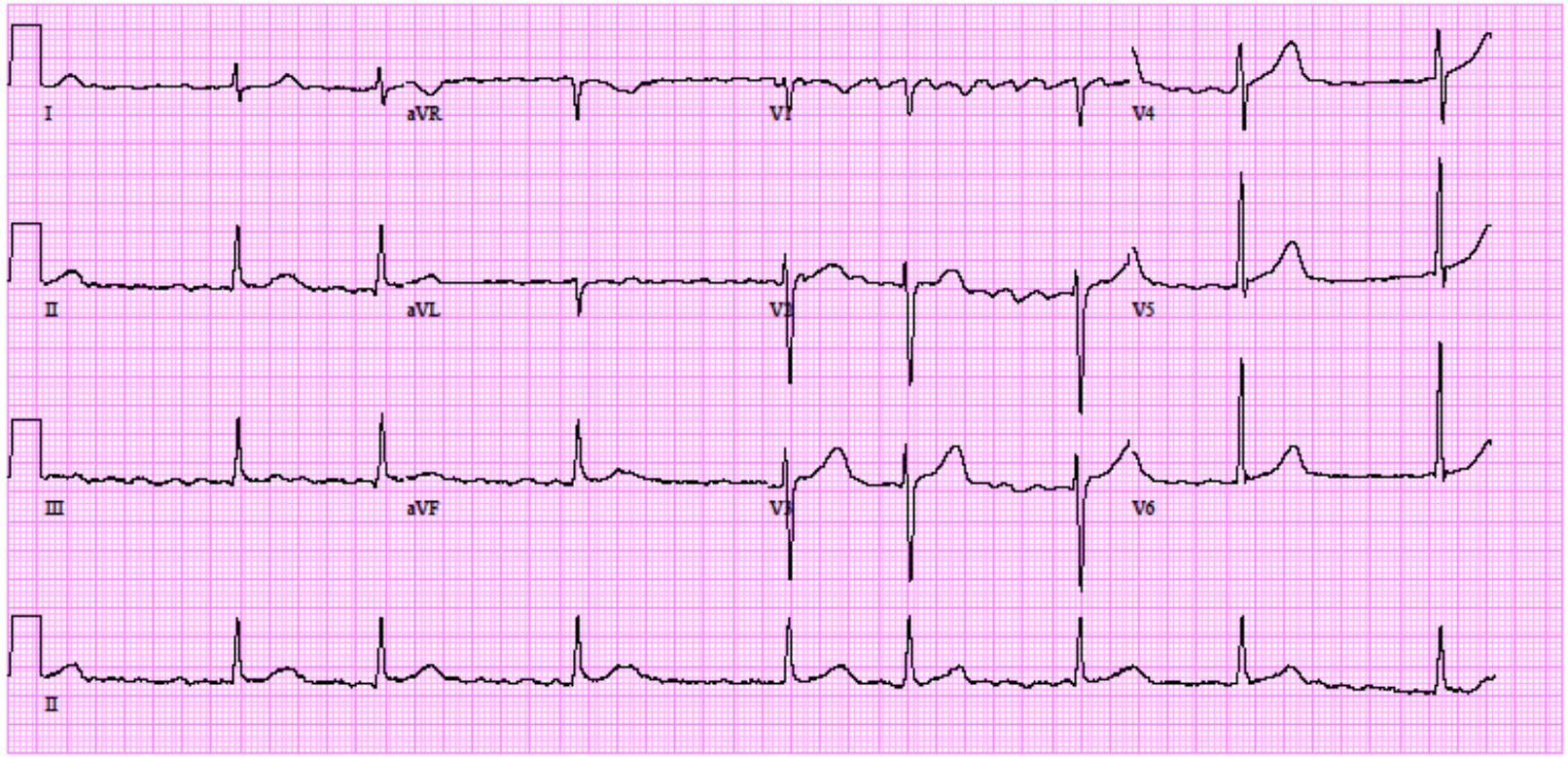
Vent. rate	51	BPM
PR interval	*	ms
QRS duration	100	ms
QT/QTc	516/475	ms
P-R-T axes	* 86	54

Atrial fibrillation with slow ventricular response
Abnormal ECG
When compared with ECG of 09-JAN-2015 09:23,
No significant change was found

Technician:
Test ind:

Med:

Referred by: Newly Acquired



25mm/s 10mm/mV 40Hz 7.1.1 12SL 239 CID: 1

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Page 1 of 1

Jeong, Yeonbeom ID:0870201 14-APR-2015 04:12:37 Kosin University Hospital

54 yr
Male Asian

Room:
Loc:14

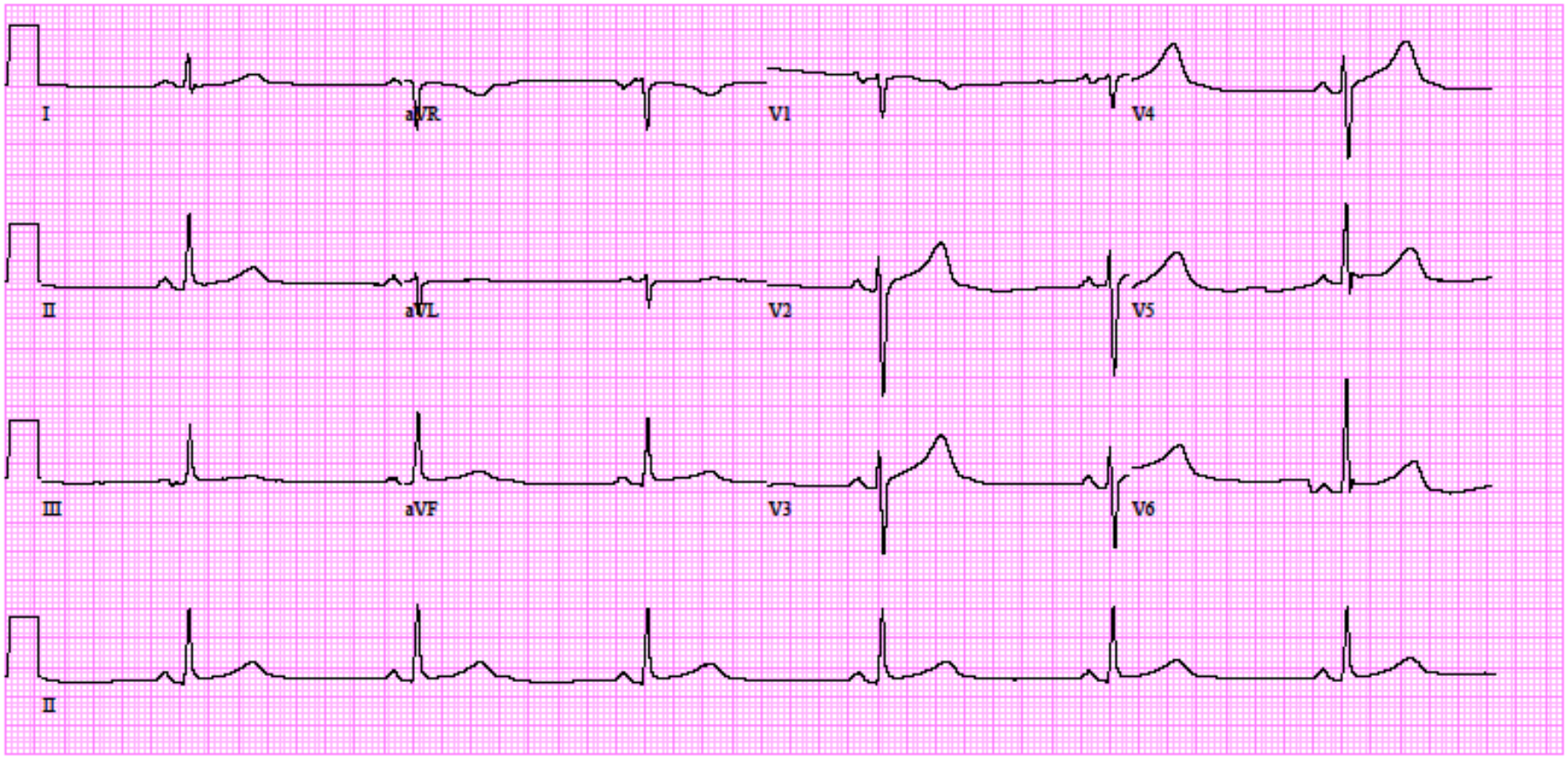
Vent. rate	38	BPM
PR interval	174	ms
QRS duration	112	ms
QT/QTc	614/488	ms
P-R-T axes	41 74	55

Marked sinus bradycardia
Prolonged QT
Abnormal ECG
When compared with ECG of 13-APR-2015 23:41,
No significant change was found

Technician:
Test ind:

Referred by:

Newly Acquired



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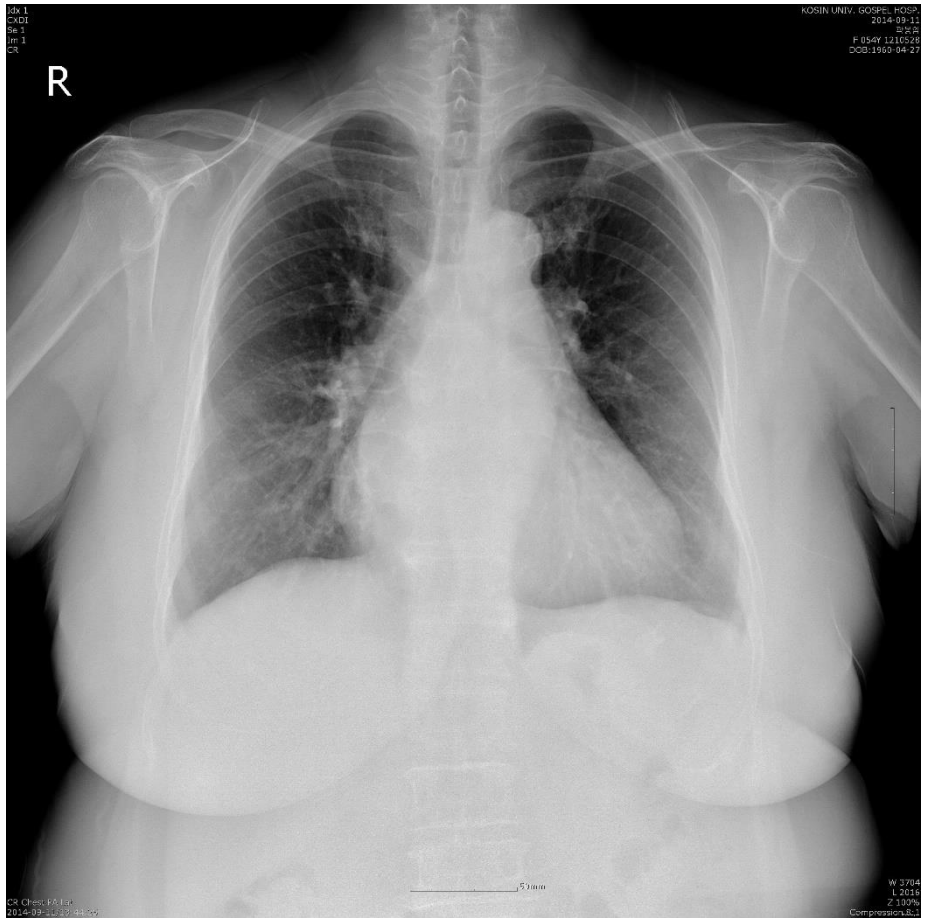
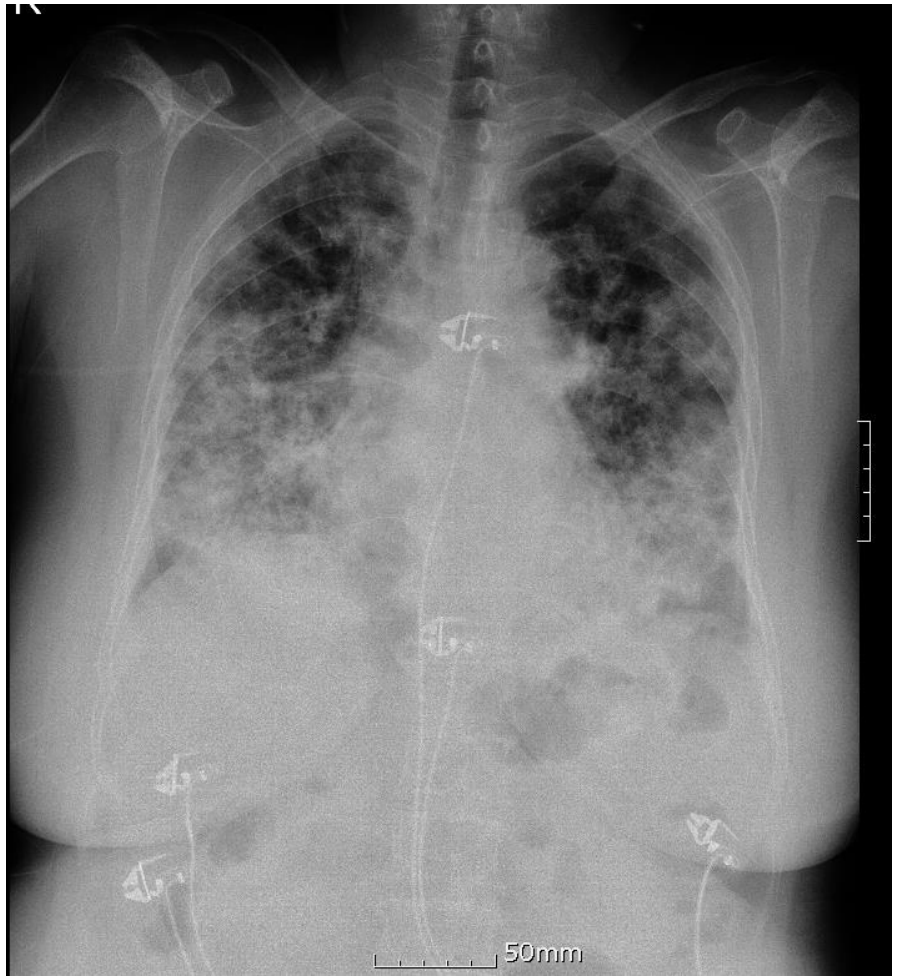
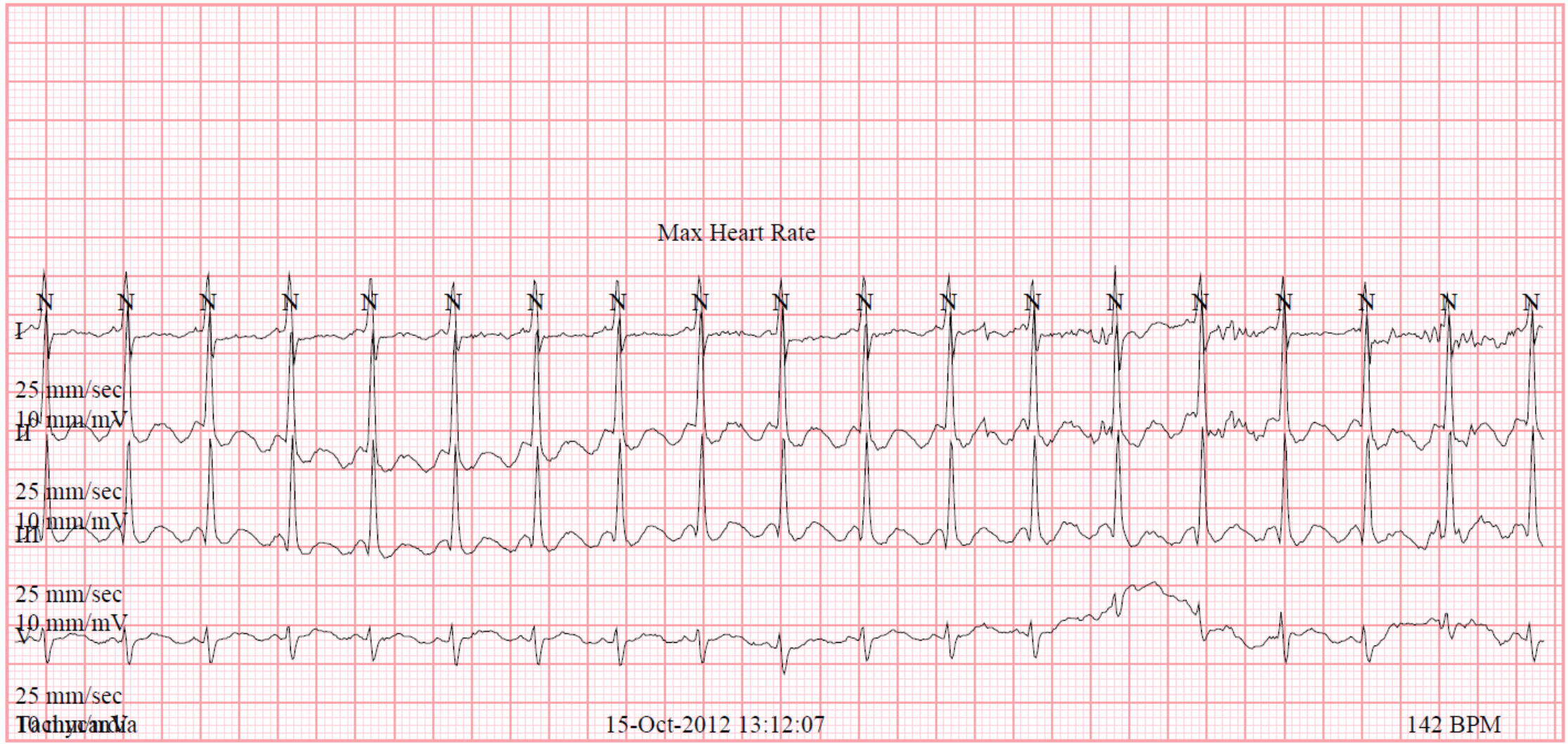
55/F 곽00, MS with AF amiodarone start 2012/oct/09
Maintenance amiodarone 100 mg/day, with warfarin



2014/Sep/11



2014/Nov/28


Max Heart Rate
N N N N N N N N N N N N N N N N N N N N
I
25 mm/sec
10 mm/mV
II
25 mm/sec
10 mm/mV
III
25 mm/sec
10 mm/mV
V
25 mm/sec
Tachycardia
15-Oct-2012 13:12:07
142 BPM

Gwak, Bongim ID:1210528 22-MAY-2012 09:23:57 Kosin University Hospital

52 yr
Female Asian

Room:
Loc:12

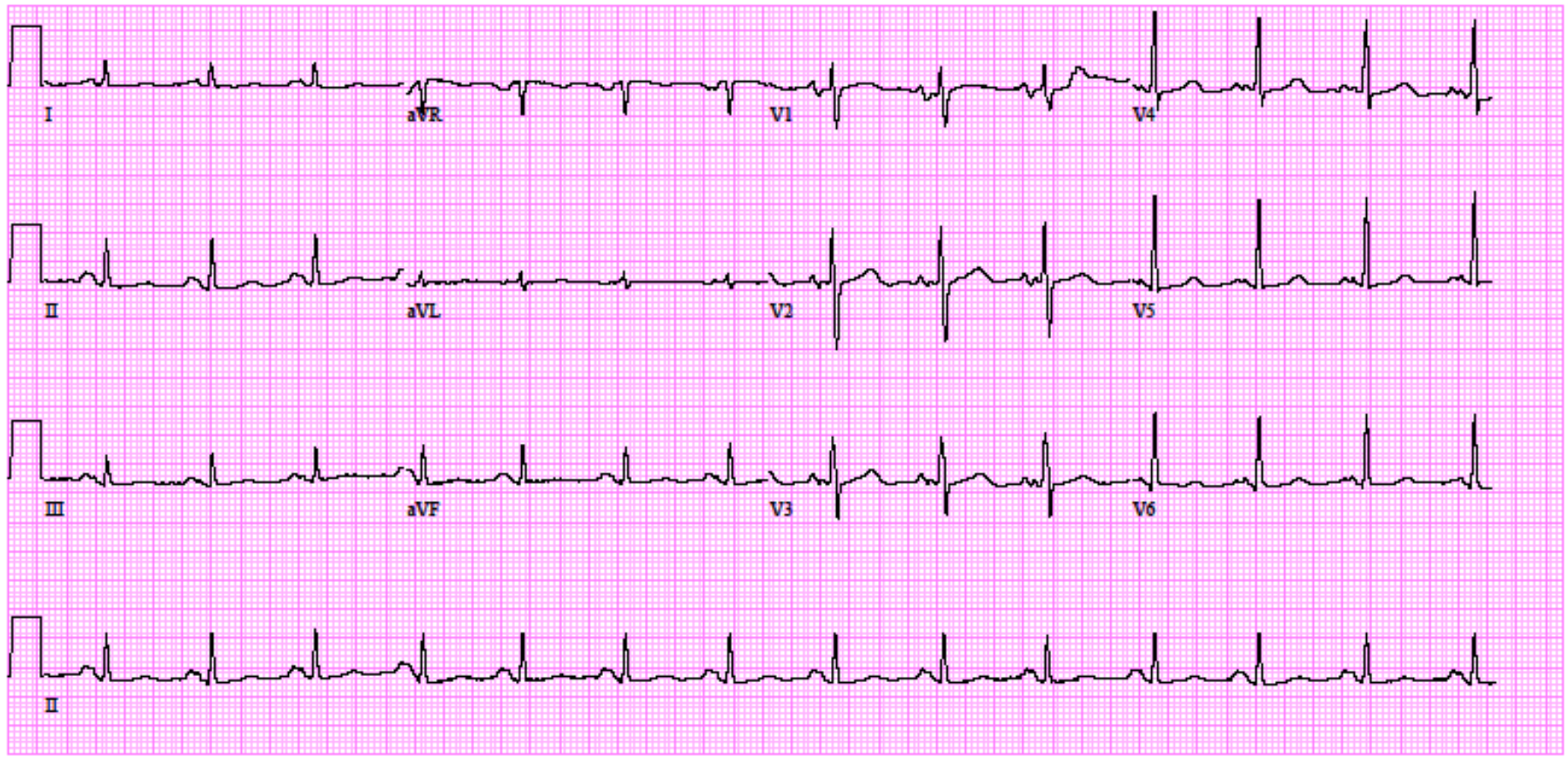
Vent. rate	83	BPM
PR interval	150	ms
QRS duration	76	ms
QT/QTc	400/470	ms
P-R-T axes	67 64	74

Normal sinus rhythm
Normal ECG
Confirmed by KIM, DA JUNG (132) on 6/3/2012 12:38:09 AM

Technician: LEE SUJIN
Test ind:

Referred by:

Confirmed By: DA JUNG KIM



25mm/s 10mm/mV 40Hz 7.1.1 12SL 237 CID: 1

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Gwak, Bongim ID:1210528 13-JUL-2014 07:47:54 Kosin University Hospital

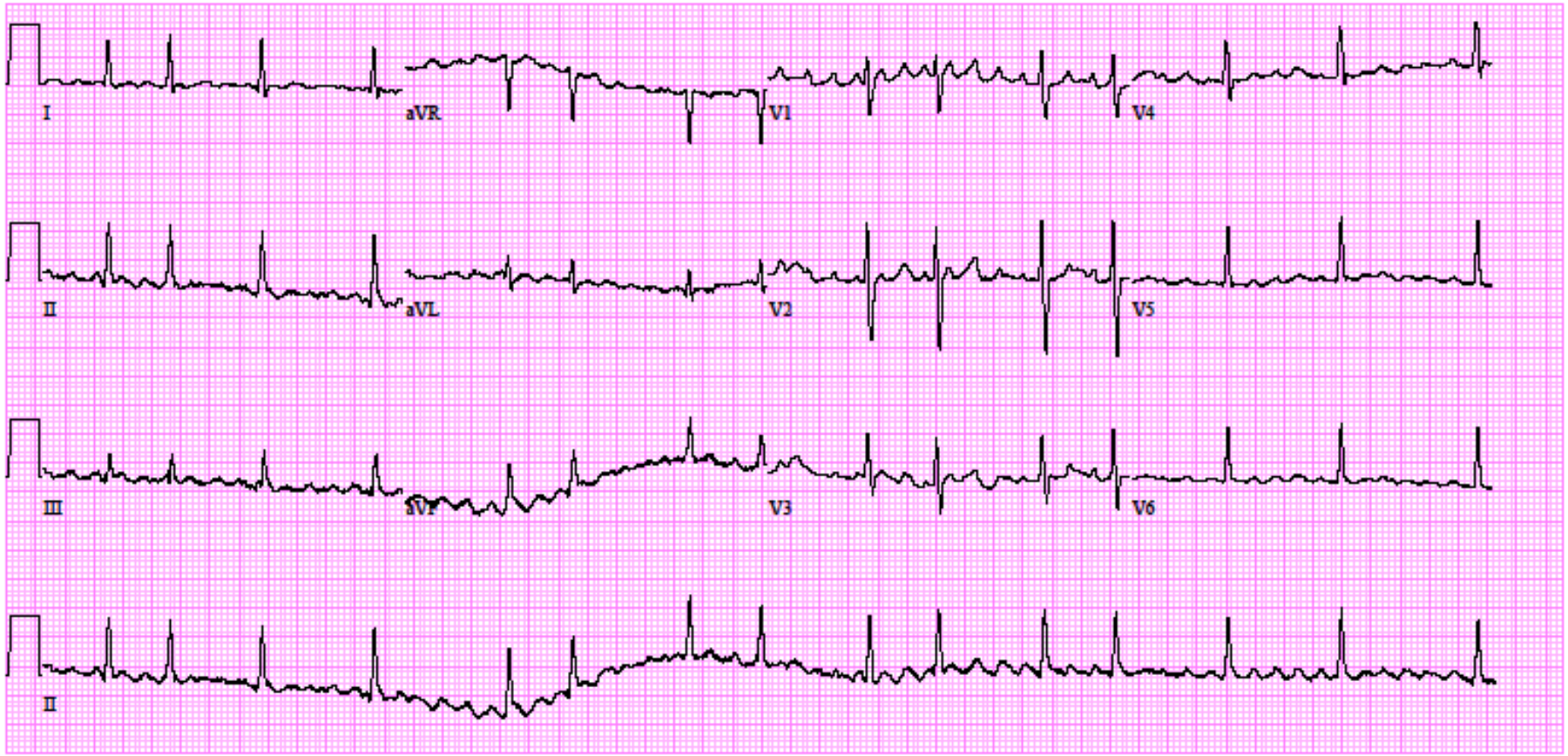
54 yr
Female Asian
0cm 0kg
Room:
Loc:14

Vent. rate	89	BPM
PR interval	*	ms
QRS duration	70	ms
QT/QTc	400/486	ms
P-R-T axes	* 50	57

*** Poor data quality, interpretation may be adversely affected
Accelerated Junctional rhythm with premature supraventricular complexes with frequent premature ventricular complexes and fusion complexes
Nonspecific ST and T wave abnormality
Prolonged QT
Abnormal ECG
When compared with ECG of 12-JUL-2014 06:06,
Junctional rhythm has replaced Atrial fibrillation
ST no longer depressed in Anterior leads
QT has lengthened

Technician:
Test ind:

Referred by: Demographics completed by: SungTaek Park



25mm/s 10mm/mV 40Hz 7.1.1 12SL 237 CID: 1

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Gwak, Bongim ID:1210528 28-NOV-2014 05:55:35 Kosin University Hospital

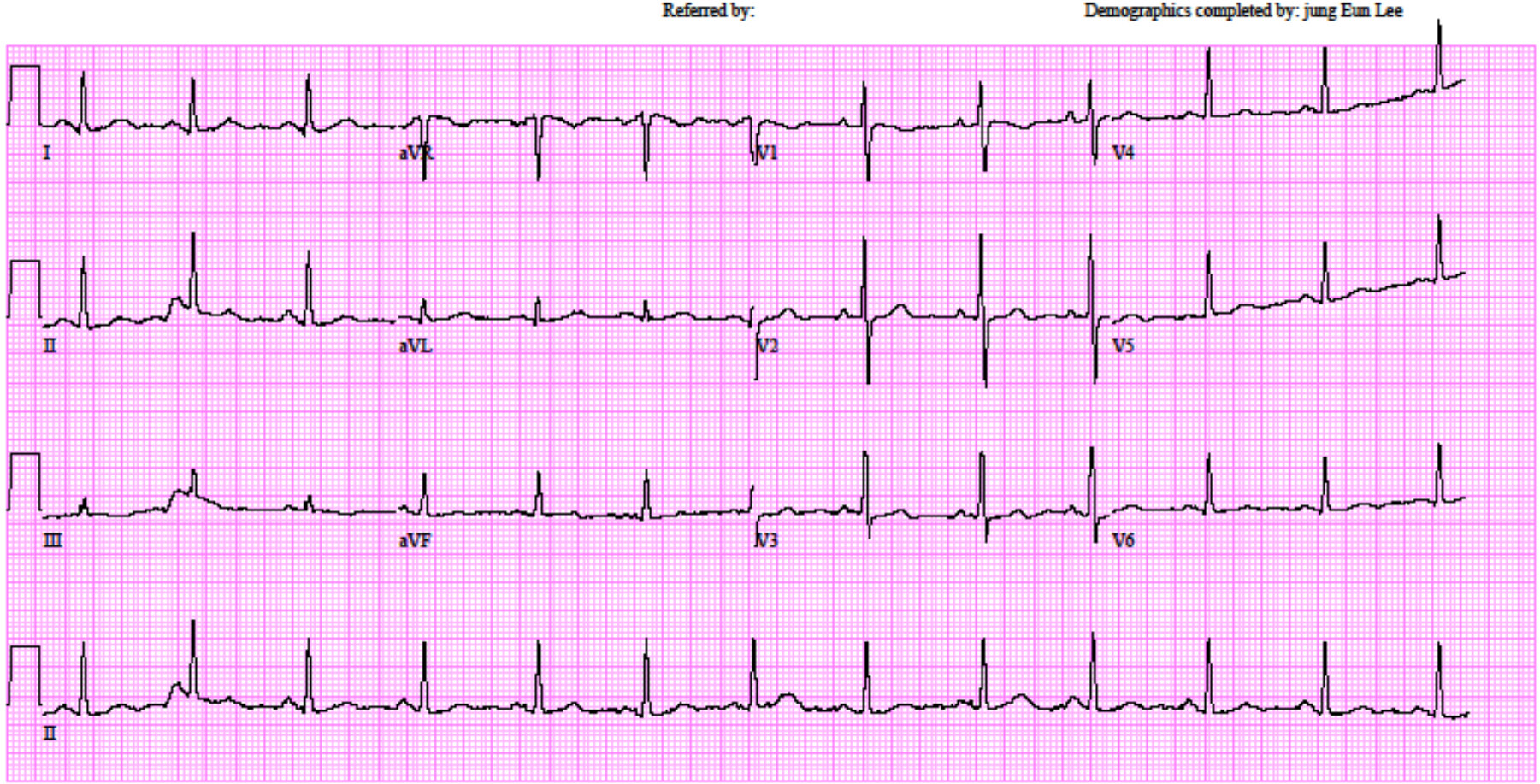
54 yr
Female Asian
0cm 0kg
Room:
Loc:14

Vent. rate	76	BPM
PR interval	158	ms
QRS duration	78	ms
QT/QTc	410/461	ms
P-R-T axes	31 46	2

Normal sinus rhythm
ST abnormality, possible digitalis effect
Abnormal ECG
When compared with ECG of 27-NOV-2014 19:02,
Nonspecific T wave abnormality, improved in Lateral leads
QT has lengthened

Technician:
Test ind:

Referred by: Demographics completed by: jung Eun Lee



25mm/s 10mm/mV 40Hz 7.1.1 12SL 237 CID: 1

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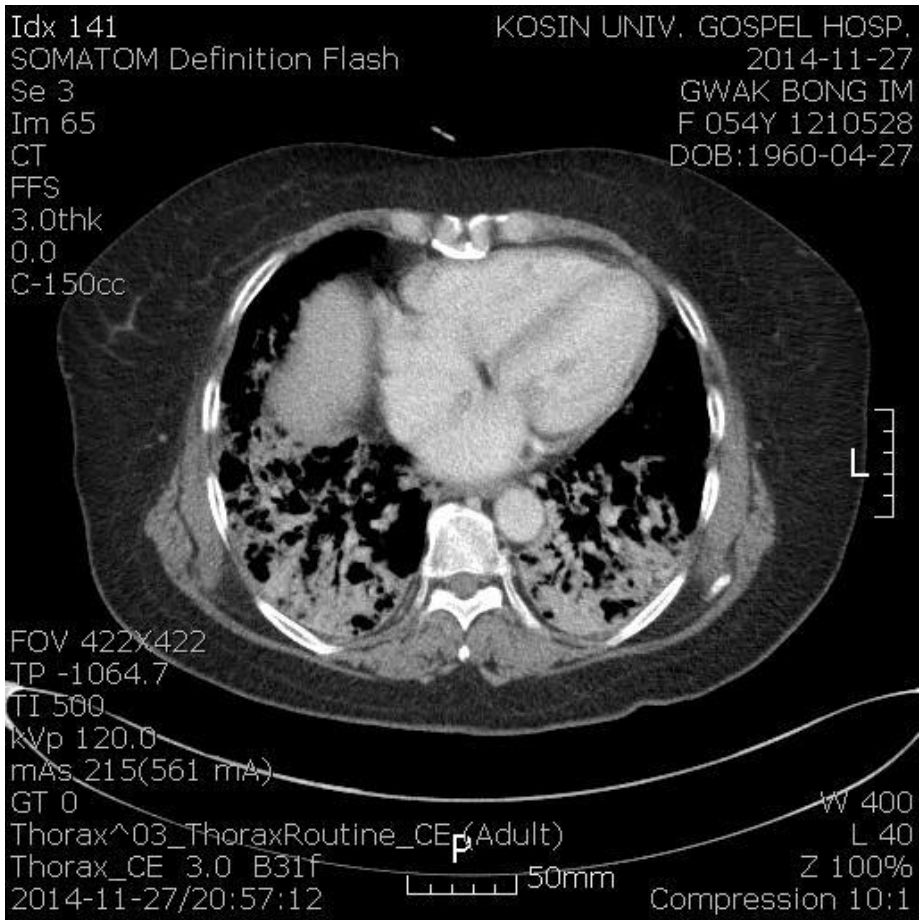
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Im 65
CT
FFS
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0.0
C-150cc
KOSIN UNIV. GOSPEL HOSP.
2014-11-27
GWAK BONG IM
F 054Y 1210528
DOB:1960-04-27
L
FOV 422X422
TP -1064.7
TI 500
kVp 120.0
mAs 215(561 mA)
GT 0
Thorax^03_ThoraxRoutine_CE (Adult)
Thorax_CE 3.0 B31f
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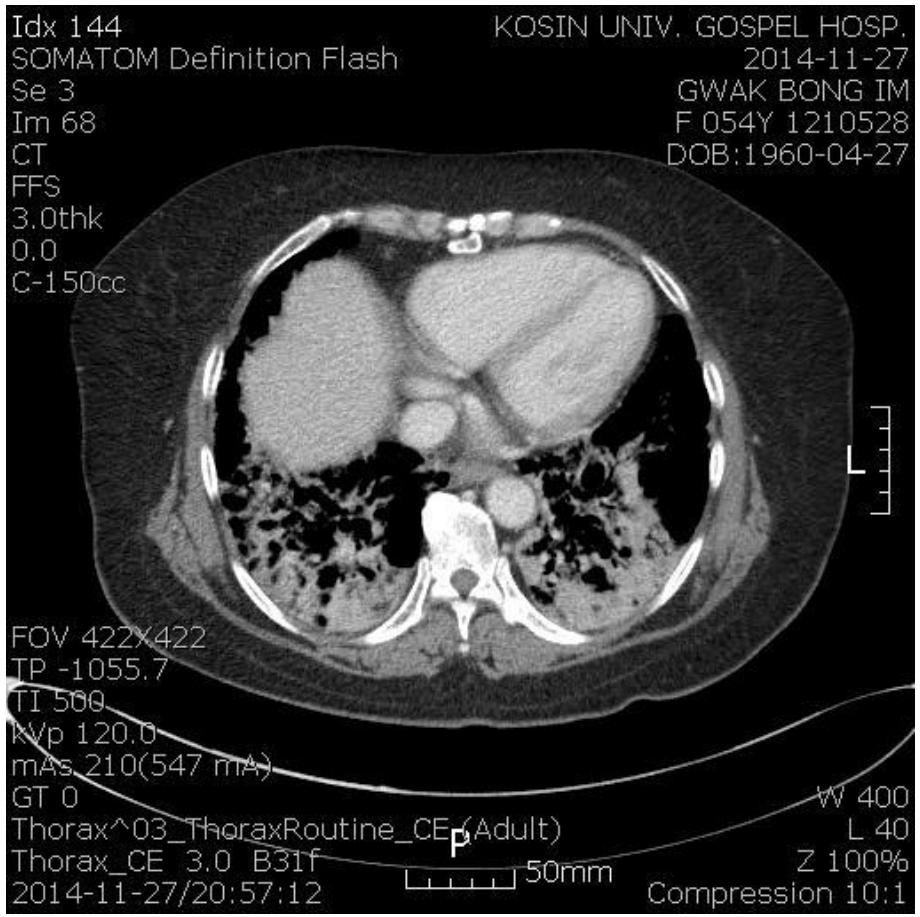
P
50mm
W 400
L 40
Z 100%
Compression 10:1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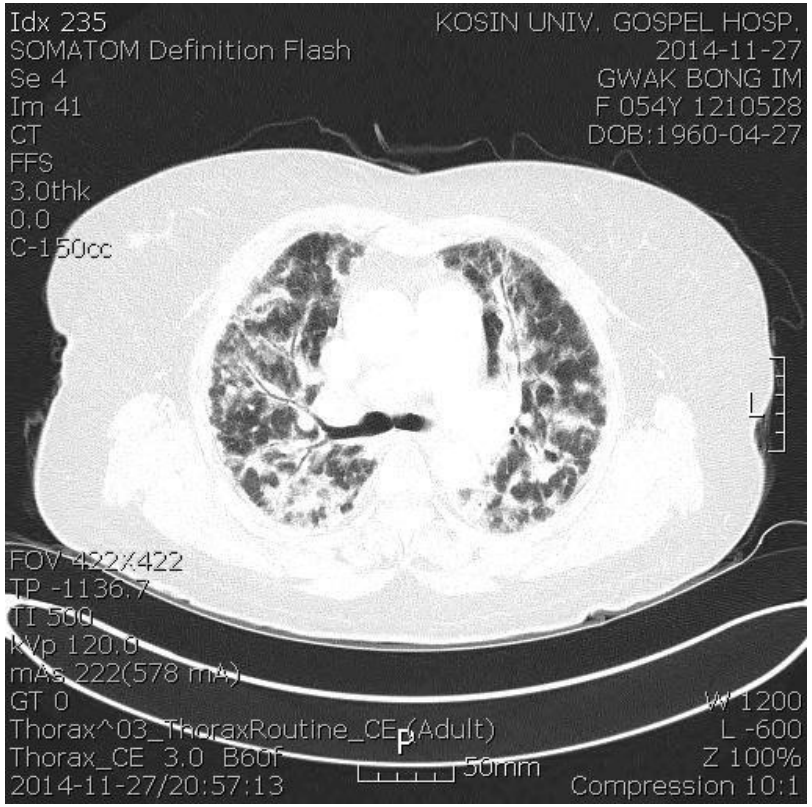
Se 3
Im 68
CT
FFS
3.0thk
0.0
C-150cc
KOSIN UNIV. GOSPEL HOSP.
2014-11-27
GWAK BONG IM
F 054Y 1210528
DOB:1960-04-27
L
FOV 422X422
TP -1055.7
TI 500
kVp 120.0
mAs 210(547 mA)
GT 0
Thorax^03_ThoraxRoutine_CE (Adult)
Thorax_CE 3.0 B31f
2014-11-27/20:57:12
P
50mm
W 400
L 40
Z 100%
Compression 10:1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2014-11-27
GWAK BONG IM
F 054Y 1210528
DOB:1960-04-27
FOV 422X422
TP -1136.7
TI 500
kVp 120.0
mAs 222(578 mA)
GT 0
Thorax^03_ThoraxRoutine_CE (Adult)
Thorax_CE 3.0 B60f
2014-11-27/20:57:13
50mm
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L -600
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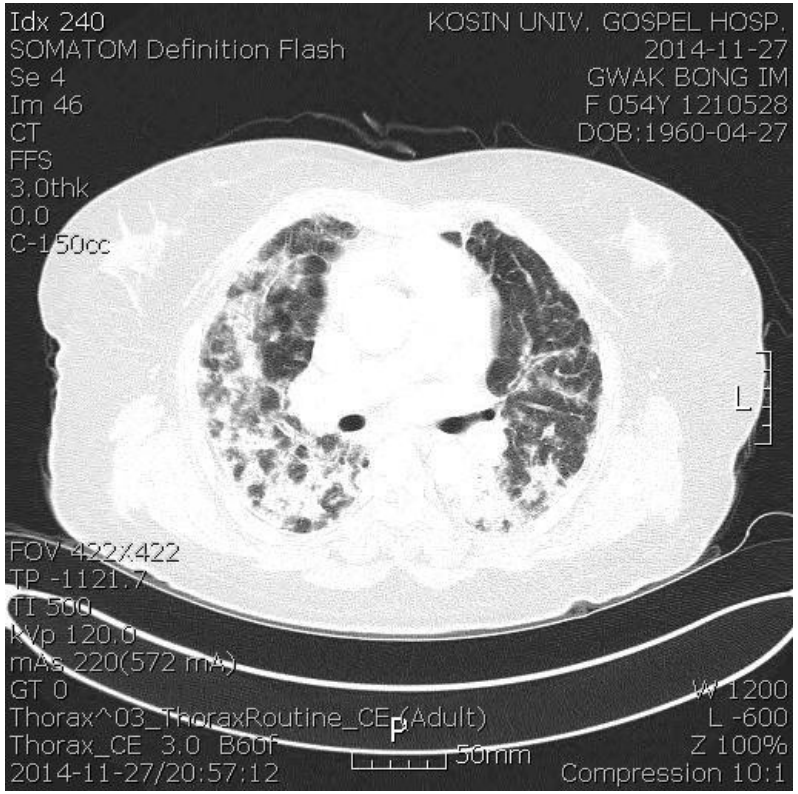
Compression 10:1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GWAK BONG IM
F 054Y 1210528
DOB:1960-04-27
FOV 422X422
TP -1121.7
TI 500
kVp 120.0
mAs 220(572 mA)
GT 0
Thorax^03_ThoraxRoutine_CE (Adult)
Thorax_CE 3.0 B60f
2014-11-27/20:57:12
50mm
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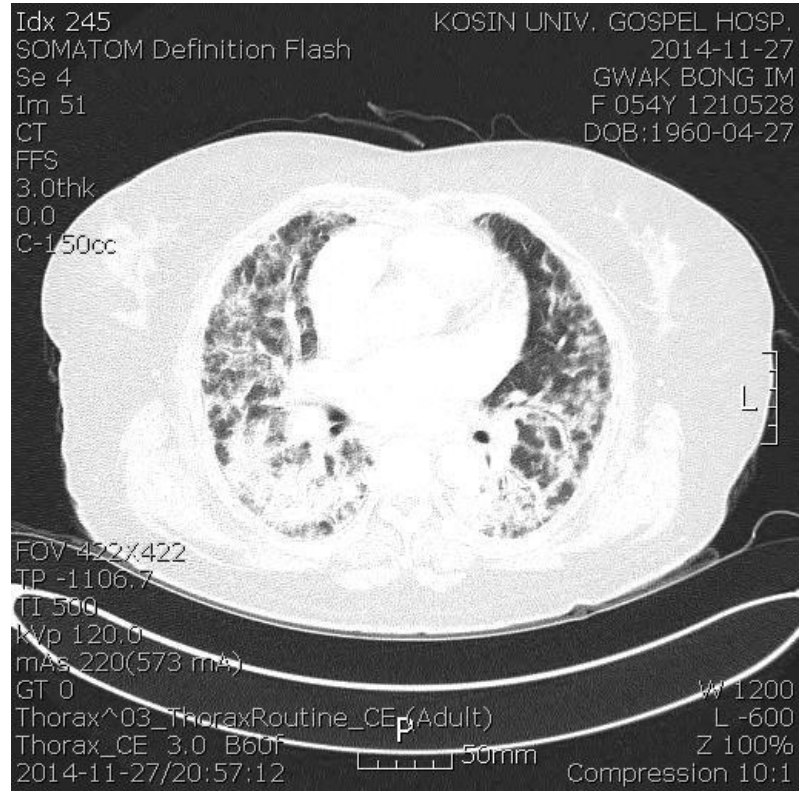
L -600
Z 100%
Compression 10:1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2014-11-27
GWAK BONG IM
F 054Y 1210528
DOB:1960-04-27
FOV 422X422
TP -1106.7
TI 500
kVp 120.0
mAs 220(573 mA)
GT 0
Thorax^03_ThoraxRoutine_CE (Adult)
Thorax_CE 3.0 B60f
2014-11-27/20:57:12
50mm
W 1200
L -600
Z 100%
Compression 10:1

Take home message

- **Flecainide is narrow therapeutic index drug,**
  - **PR interval ≥ 40 ms, QRS ≥ 40 ms suggest high drug concentration, impending cardiovascular side effects**
  - **Cix in RBBB with hemi fascicular block**
- **Propafenone have beta blocking effect**
  - **Not recommend in rate dependent bundle branch block**
- **Drug toxicity of 1c agents can be early detected by exercise test.**
- **Amiodarone is not safe drug when it use with warfarine.**

감사합니다.