Amiodarone is Associated with Increased Mortality Compared with Other Antiarrhythmic Drugs in New-onset Atrial Fibrillation Patients

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COI Disclosure

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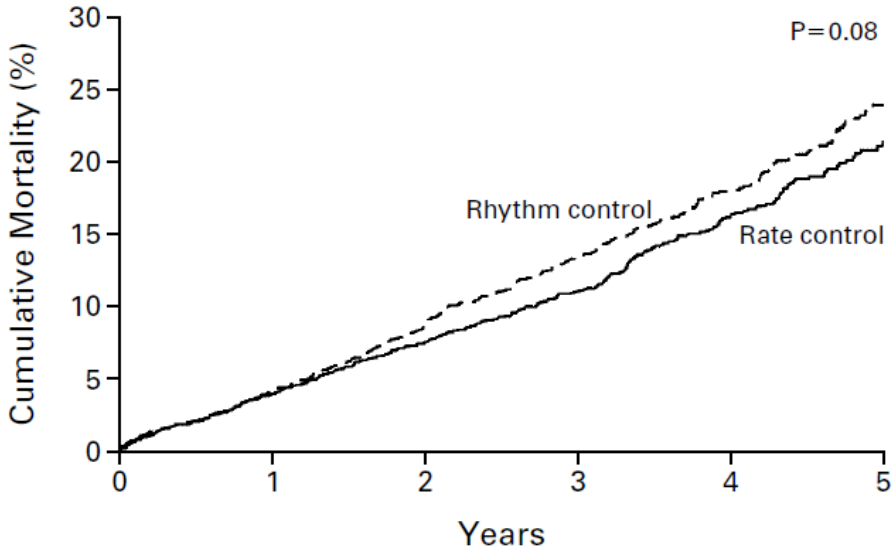
The authors have no financial conflicts of interest to disclose concerning the presentation

Agenda

- Introduction
- Methods
- Results
- Discussion
- Conclusion

Introduction

the AFFIRM trial

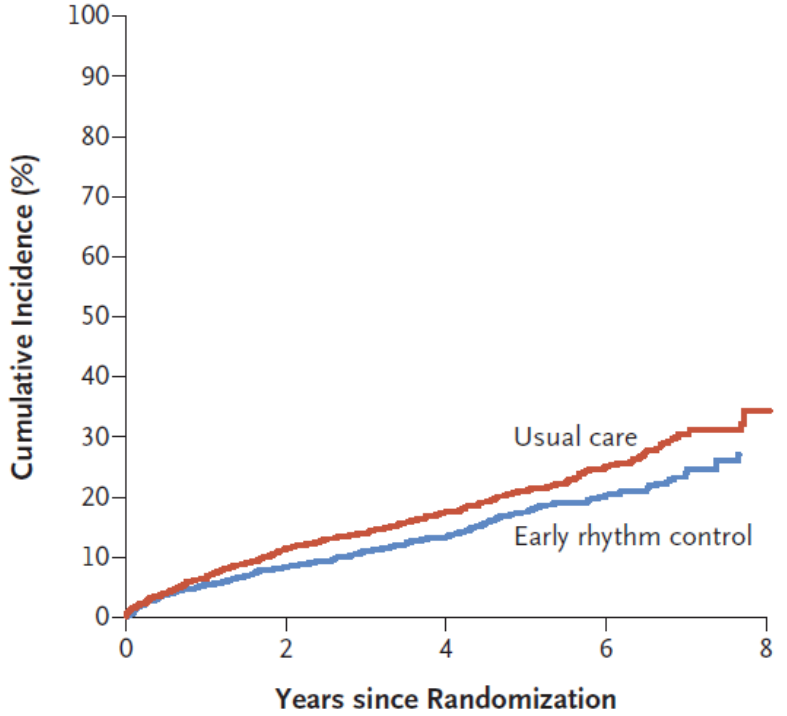


No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.
Time zero is the day of randomization. Data have been truncated at five years.

Van Gelder IC et el. *N Egnl J Med* 2002;347:1825-33.

the EAST-AFNET 4 trial



No. at Risk					
Usual care	1394	1169	888	405	34
Early rhythm control	1395	1193	913	404	26

P. Kirchhof et el. *N Egnl J Med* 2020;383:14.

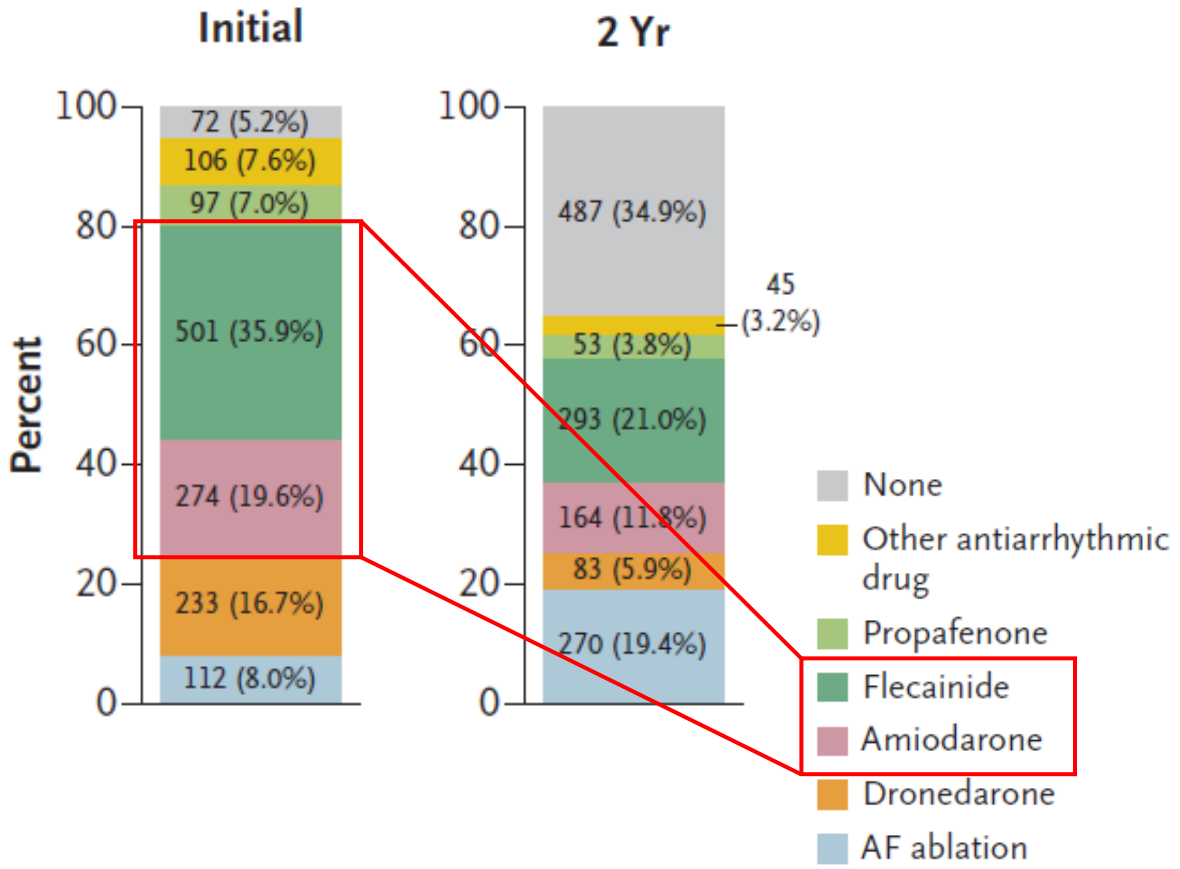
Introduction

the AFFIRM trial

Drug	Rate-Control Group		Rhythm-Control Group	
	Used drug for initial therapy	Used drug at any time	Used drug for initial therapy	Used drug at any time
	no. of patients (%)			
Rate control				
Data available	1957	2027	1266	2033
Digoxin	949 (48.5)	1432 (70.6)	417 (32.9)	1106 (54.4)
Beta-blocker	915 (46.8)	1380 (68.1)	276 (21.8)	1008 (49.6)
Diltiazem	583 (29.8)	935 (46.1)	198 (15.6)	610 (30.0)
Verapamil	187 (9.6)	340 (16.8)	56 (4.4)	204 (10.0)
Rhythm control				
Data available	1265	2027	1960	2033
Amiodarone	2 (0.2)†	207 (10.2)	735 (37.5)	1277 (62.8)
Sotalol	1 (0.1)†	84 (4.1)	612 (31.2)	841 (41.4)
Propafenone	2 (0.2)†	45 (2.2)	183 (9.3)	294 (14.5)
Procainamide	0	30 (1.5)	103 (5.3)	173 (8.5)
Quinidine	2 (0.2)†	14 (0.7)	92 (4.7)	151 (7.4)
Flecainide	0	29 (1.4)	88 (4.5)	169 (8.3)
Disopyramide	0	7 (0.3)	42 (2.1)	87 (4.3)
Moricizine	0	2 (0.1)	14 (0.7)	35 (1.7)
Dofetilide	0	5 (0.2)	0	13 (0.6)

Van Gelder IC et el. *N Egnl J Med* 2002;347:1825-33.

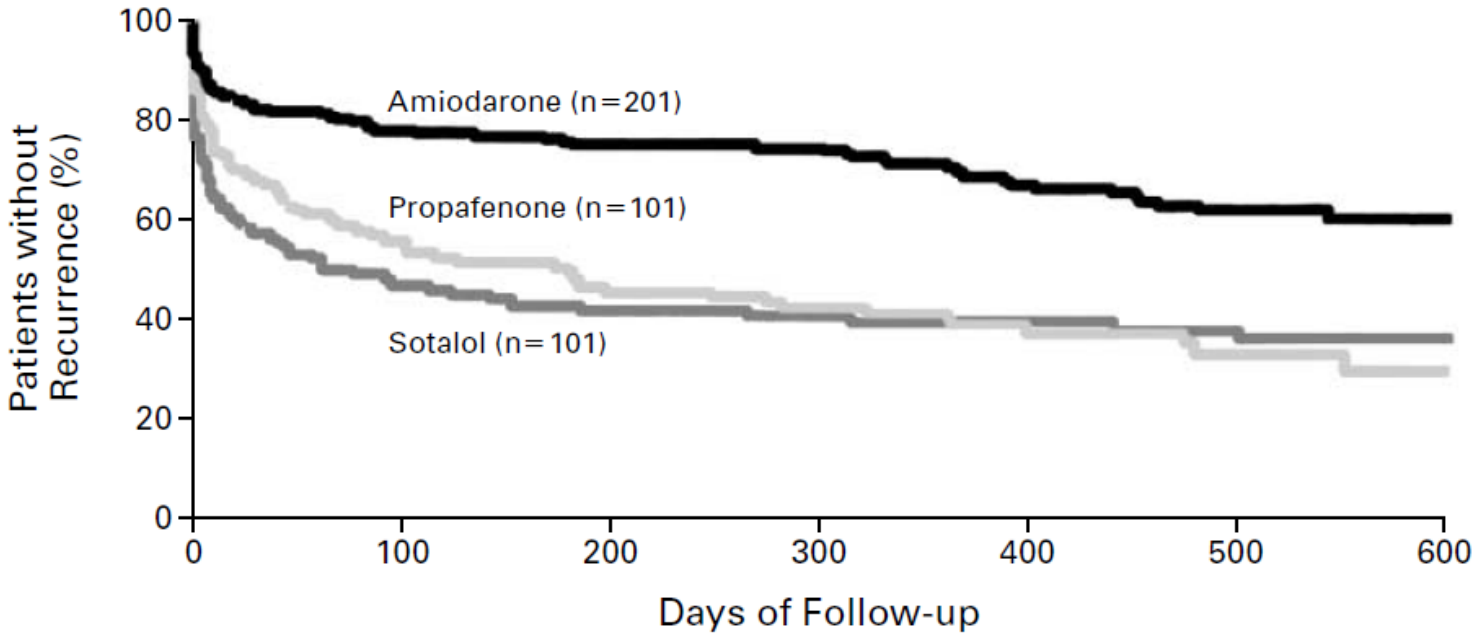
the EAST-AFNET 4 trial

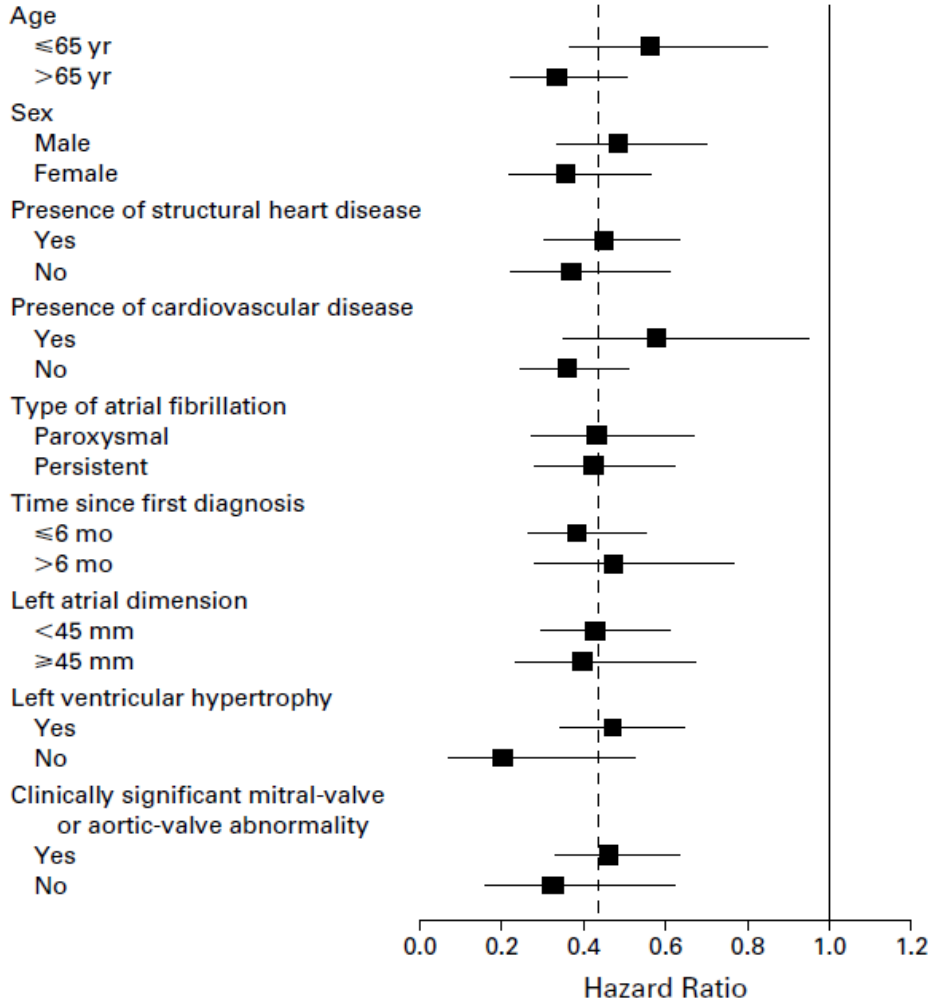


P. Kirchhof et el. *N Egnl J Med* 2020;383:14.

KHRS 2023

Introduction





Denis Roy et el. *N Egnl J Med* 2000;342:913-20.

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Introduction

Table 1. Adverse Effects of Oral Amiodarone.

Adverse Effect	Incidence	Recommended Monitoring	Special Considerations
Cardiac		Baseline electrocardiogram at least once during loading period, especially if conduction disease is present; yearly thereafter	Consider reduction of loading dose in elderly patients and those with underlying sinoatrial or atrioventricular conduction disease; reduce dose or discontinue if QT interval exceeds 550 msec
Bradycardia	5%		
Prolonged QT interval	In most patients		
Torsades de pointes	<1%		
Hepatic	15%	Aspartate and alanine aminotransferase measurements at baseline and every 6 months thereafter	Avoid in patients with severe liver disease
Thyroid		Thyroid-function tests at baseline and two or three times a year thereafter	Avoid in presence of preexisting, nonfunctioning thyroid nodule; higher incidence of thyroid effects in patients with autoimmune thyroid disease
Hyperthyroidism	3%		
Hypothyroidism	20%		
Pulmonary	<3%	Pulmonary-function tests at baseline and if symptoms develop; chest radiograph at baseline and yearly thereafter	Discontinue amiodarone immediately if pulmonary effects suspected
Dermatologic	25–75%	Routine	Recommend use of sunscreen with a high sun protection factor
Neurologic	3–30%	Routine	Consider dose reduction
Ophthalmologic		Examination at baseline if there is underlying abnormality; examinations as needed thereafter	Avoid in presence of preexisting optic neuritis
Corneal deposits	100%		
Optic neuritis	<1%		

Peter Zimetbaum. *N Egnl J Med* 2007;356:935-41.

Introduction

Is amiodarone associated with increased mortality?

Peter Zimetbaum. *N Egnl J Med* 2007;356:935-41.

Methods

- Data from the Korean National Health Insurance Service (K-NHIS)

  - All cause death

  - Diagnosis of AF

  - Prescription of AAD

  - Underlying disease such as DM, HTN, Dyslipidemia, HF, MI, CKD, thyroid disease, and stroke

- Data from Nationwide health screening

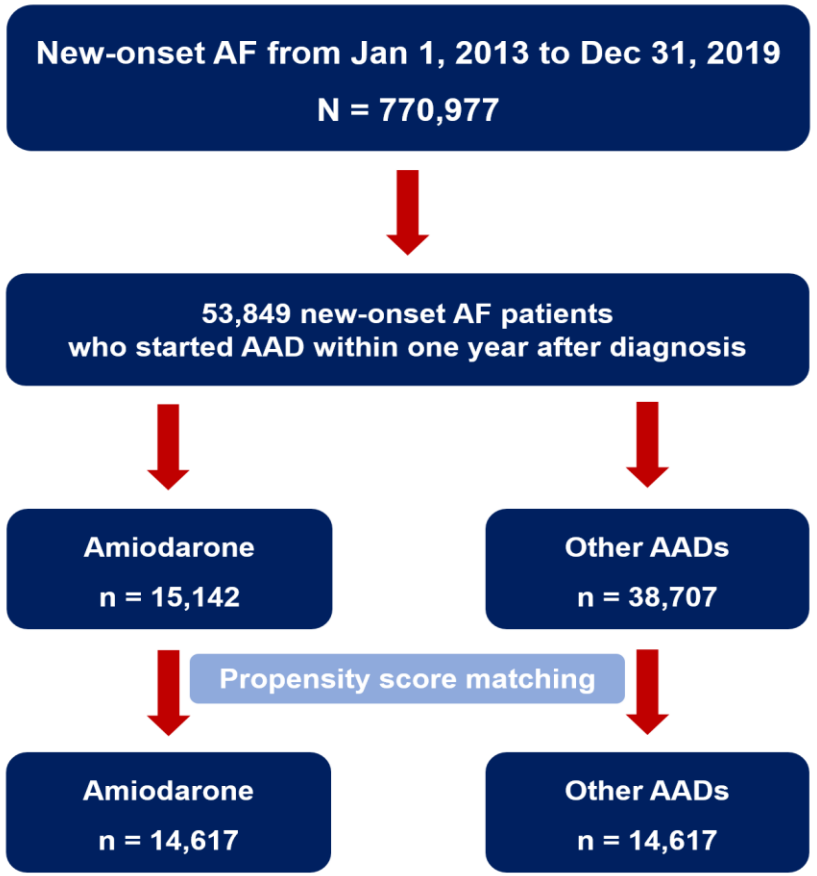
  - medical measurements such as blood pressure, body weight, and stature

  - self-report questionnaires regarding smoking status, alcohol consumption habits, and exercise level

  - laboratory tests such as complete blood cell counts, serum creatinine level, liver function tests, lipid profiles, and fasting blood glucose

Methods

- Primary outcome endpoint : All-cause death
- Flow of the study



Exclusion

- Patients were younger than 18 years: 6,832
- History of syncope or pacemaker: 51,471
- History of ventricular tachycardia or ventricular fibrillation: 11,501
- Patients who received amiodarone and other AADs alternatively: 18,029
- Medication possession ratio < 0.5: 91,036
- Patients who didn't receive any AADs: 538,259

Results Baseline demographics

	Before PSM					After PSM		
	AAD (+)	Amiodarone	Other AADs	p value		Amiodarone	Other AADs	p value
N	53,849	15,142	38,707			14,167	14,167	
Age group				< 0.001				0.359
– 39	1,477 (2.7%)	262 (1.7%)	1,215 (3.1%)			262 (1.8%)	247 (1.7%)	
40 – 64	23,951 (44.5%)	5,487 (36.2%)	18,464 (47.7%)			5,390 (36.9%)	5,292 (36.2%)	
65 –	28,421 (52.8%)	9,393 (62.0%)	19,028 (49.2%)			8,965 (61.3%)	9,078 (62.1%)	
Sex				< 0.001				0.625
Male	32,297 (60.0%)	8,950 (59.1%)	23,347 (60.3%)			8,739 (59.8%)	8,581 (58.7%)	
Female	21,552 (40.0%)	6,192 (40.9%)	15,360 (39.7%)			5,878 (40.2%)	6,036 (41.3%)	
Current smoker*				< 0.001				< 0.001
Non smoker	18,734 (34.8%)	4,938 (32.6%)	13,796 (35.6%)			4,847 (33.2%)	4,838 (33.1%)	
Former smoker	8,708 (16.2%)	2,098 (13.9%)	6,610 (17.1%)			2,066 (14.1%)	2,293 (15.7%)	
Current smoker	5,007 (9.3%)	1,442 (9.5%)	3,565 (9.2%)			1,429 (9.8%)	1,168 (8.0%)	
Missing value	21,400 (39.7%)	6,664 (44.0%)	14,736 (38.1%)			6,275 (42.9%)	6,318 (43.2%)	

	Before PSM				After PSM		
	AAD (+)	Amiodarone	Other AADs	p value	Amiodarone	Other AADs	p value
n	53,849	15,142	38,707		14,167	14,167	
Alcohol consumption*				< 0.001			0.973
Non	19,216 (35.7%)	5,261 (34.7%)	13,955 (36.1%)		5,165 (35.3%)	5,165 (35.3%)	
Mild to moderate	10,637 (19.7%)	2,546 (16.8%)	8,091 (20.9%)		2,512 (17.2%)	2,515 (17.2%)	
Heavy	2,558 (4.8%)	660 (4.4%)	1,898 (4.9%)		652 (4.5%)	651 (4.5%)	
Missing value	21,438 (39.8%)	6,675 (44.1%)	14,763 (38.1%)		6,323 (43.3%)	6,286 (43.0%)	
Regular exercise				< 0.001			0.482
Yes	20,777 (38.6%)	5,628 (37.2%)	15,149 (39.1%)		5,530 (37.8%)	5,435 (37.2%)	
No	11,669 (21.7%)	2,849 (18.8%)	8,820 (22.8%)		2,811 (19.2%)	2,864 (19.6%)	
Missing value	21,403 (39.7%)	6,665 (44.0%)	14,738 (38.1%)		6,276 (42.9%)	6,318 (43.2%)	
Income quartile				< 0.001			0.824
Q1 (lowest income)	10,984 (20.4%)	3,512 (23.2%)	7,472 (19.3%)		3,351 (22.9%)	3,371 (23.1%)	
Q2	8,178 (15.2%)	2,353 (15.5%)	5,825 (15.0%)		2,274 (15.6%)	2,270 (15.5%)	
Q3	11,805 (21.9%)	3,334 (22.0%)	8,471 (21.9%)		3,236 (22.1%)	3,166 (21.7%)	
Q4 (highest income)	22,039 (40.9%)	5,688 (37.6%)	16,351 (42.2%)		5,504 (37.7%)	5,570 (38.1%)	
Missing value	843 (1.6%)	255 (1.7%)	588 (1.5%)		252 (1.7%)	240 (1.6%)	
Diabetes mellitus	8,593 (16.0%)	2,852 (18.8%)	5,741 (14.8%)	< 0.001	2,706 (18.5%)	2,672 (18.3%)	0.608
Hypertension	22,952 (42.6%)	6,381 (42.1%)	16,571 (42.8%)	0.009	6,135 (42.0%)	6,234 (42.6%)	0.241

	Before PSM				After PSM		
	AAD (+)	Amiodarone	Other AADs	p value	Amiodarone	Other AADs	p value
N	53,849	15,142	38,707		14,167	14,167	
Dyslipidemia	4,179 (7.8%)	819 (5.4%)	3,360 (8.7%)	< 0.001	815 (5.6%)	794 (5.4%)	0.590
Heart failure	1,584 (2.9%)	965 (6.4%)	619 (1.6%)	< 0.001	620 (4.2%)	602 (4.1%)	0.599
Myocardial infarction	929 (1.7%)	599 (4.0%)	330 (0.9%)	< 0.001	376 (2.6%)	328 (2.2%)	0.067
Chronic kidney disease	1,162 (2.2%)	506 (3.3%)	656 (1.7%)	< 0.001	464 (3.2%)	448 (3.1%)	0.590
Hypo- or hyper-thyroidism	1,732 (3.2%)	365 (2.4%)	1,367 (3.5%)	< 0.001	360 (2.5%)	341 (2.3%)	0.468
Stroke	2,902 (5.4%)	938 (6.2%)	1,964 (5.1%)	< 0.001	898 (6.1%)	908 (6.2%)	0.808
Age	64.8 ± 12.1	67.7 ± 12.1	63.7 ± 11.9	< 0.001	67.5 ± 12.1	66.3 ± 11.6	< 0.001
Fasting glucose (mg/dL)*	105.0 ± 26.1	107.7 ± 30.2	104.0 ± 24.4	< 0.001	107.7 ± 30.2	105.2 ± 25.9	< 0.001
Body mass index (kg/m^2)*	24.9 ± 3.3	25.0 ± 3.5	24.8 ± 3.3	< 0.001	25.0 ± 3.5	24.8 ± 3.3	< 0.001
Waist circumference (cm)*	85.2 ± 9.0	86.0 ± 9.3	85.0 ± 8.9	< 0.001	86.0 ± 9.3	85.2 ± 8.8	< 0.001
Systolic blood pressure (mmHg)*	127.2 ± 15.4	128.2 ± 16.1	126.9 ± 15.1	< 0.001	128.1 ± 16.1	127.8 ± 15.4	0.216
Diastolic blood pressure (mmHg)*	77.5 ± 10.3	77.7 ± 10.6	77.5 ± 10.1	0.099	77.7 ± 10.5	77.3 ± 10.2	0.009
eGFR*	82.5 ± 26.5	79.5 ± 26.7	83.6 ± 26.3	0.005	79.6 ± 26.6	81.7 ± 23.2	< 0.001
Total cholesterol (mg/dL)*	187.4 ± 43.9	184.5 ± 45.8	188.5 ± 43.1	< 0.001	184.6 ± 45.8	185.7 ± 42.5	0.117
MPR	0.90 ± 0.15	0.88 ± 0.16	0.91 ± 0.14	< 0.001	0.90 ± 0.20	0.90 ± 0.10	< 0.001

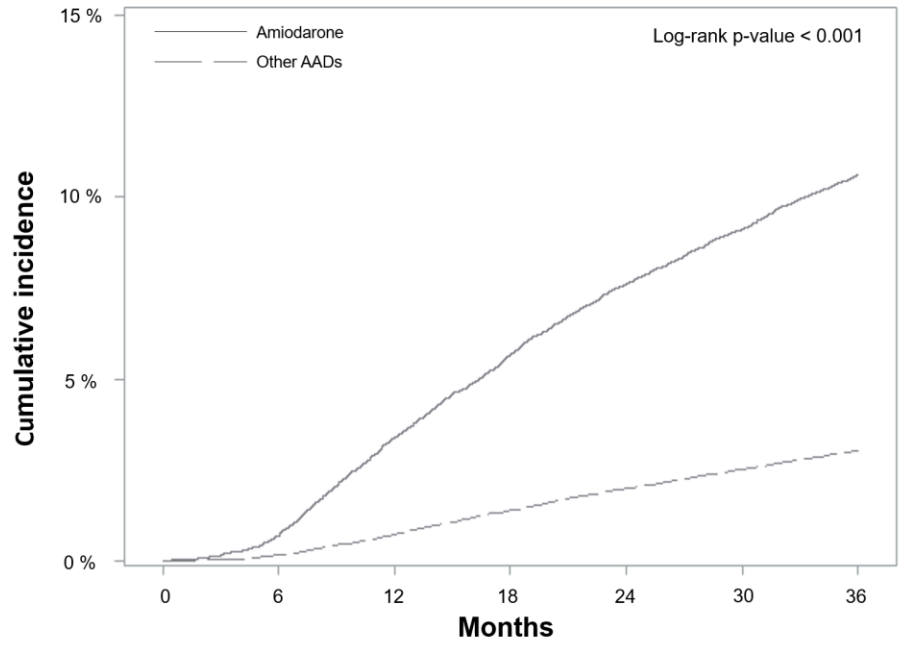
Results Amiodarone vs. other AADs for all-cause death

	n	Event number (all-cause death)	Duration (person*year)	Incidence (95% CI)	Model 1	Model 2	Model 3	Model 4	Model 5
Before PSM									
other AADs	38,707	1,178	114,517	10.3 (9.7 – 10.9)	reference	reference	reference	reference	reference
Amiodarone	15,142	1,609	43,018	37.4 (35.6 – 39.3)	3.65 (3.38 – 3.93)	3.13 (2.90 – 3.38)	2.87 (2.65 – 3.09)	2.89 (2.67 – 3.13)	3.59 (2.82 – 4.57)
After PSM									
other AADs	14,617	548	43,111	12.7 (11.7 – 13.8)	reference	reference	reference	reference	reference
Amiodarone	14,617	1,452	41,769	34.8 (33.0 – 36.6)	2.74 (2.49 – 3.03)	2.80 (2.54 – 3.09)	2.82 (2.55 – 3.12)	2.43 (2.10 – 2.81)	4.51 (2.76 – 7.38)

- Model 1: non-adjusted.
- Model 2: age and sex.
- Model 3: age, sex, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, heart failure, myocardial infarction, and thyroid disease.
- Model 4: model 3 + alcohol, smoking, body mass index, regular exercise, estimated glomerular filtration rate, and total cholesterol.
- Model 5: model 3 + AAD as a time-varying covariate
- AAD: antiarrhythmic drug; PSM: propensity-score matching.

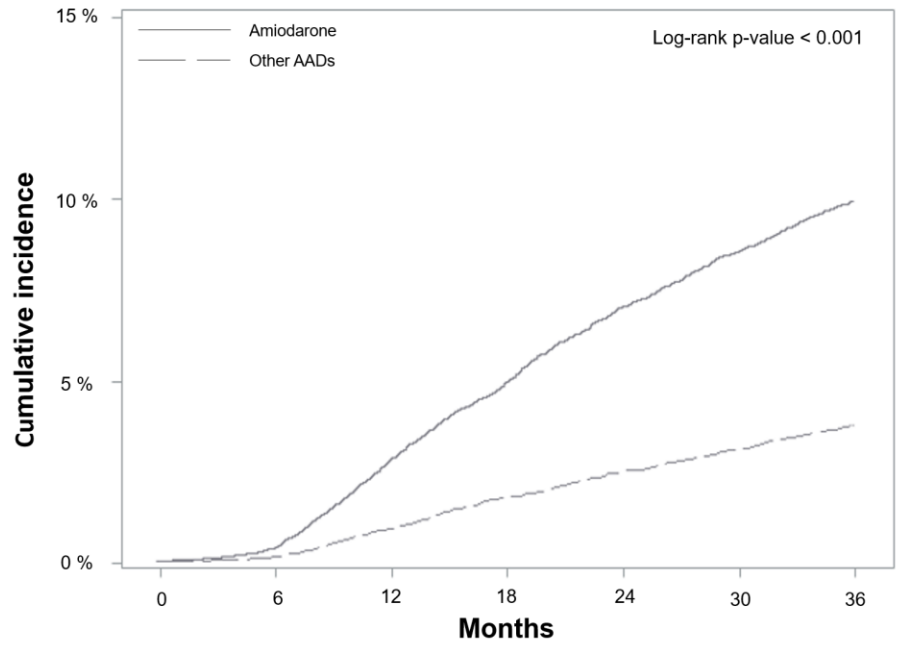
Results Cumulative incidence of all-cause death

A



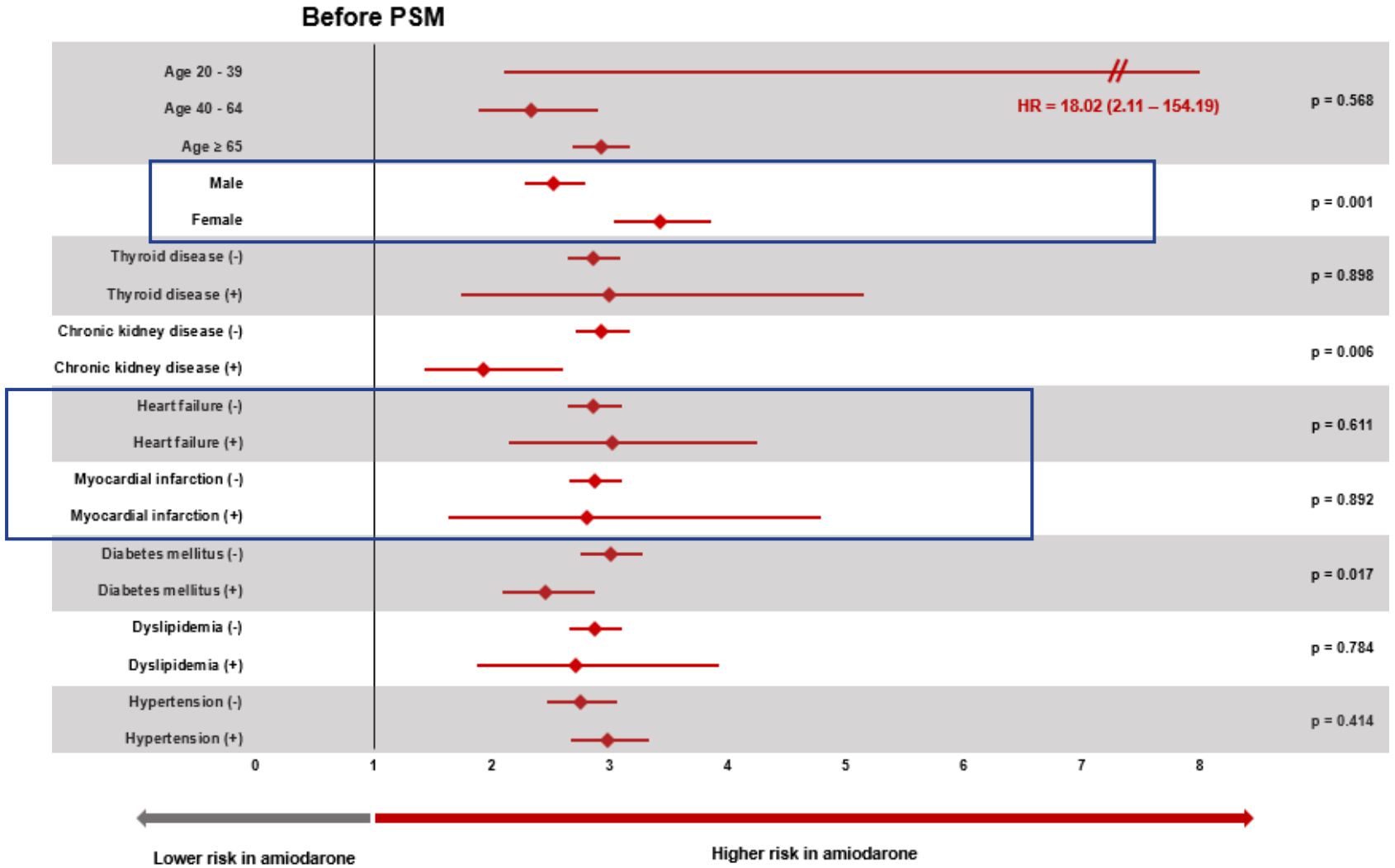
No. at Risk							
Amiodarone	15,142	15,035	14,630	14,283	13,990	13,763	13,533
Other AADs	38,707	38,639	38,424	38,171	37,938	37,731	37,529

B



No. at Risk							
Amiodarone	14,617	14,566	14,214	13,904	13,595	13,369	13,165
Other AADs	14,617	14,600	14,487	14,362	14,257	14,165	14,069

Results Subgroup analyses



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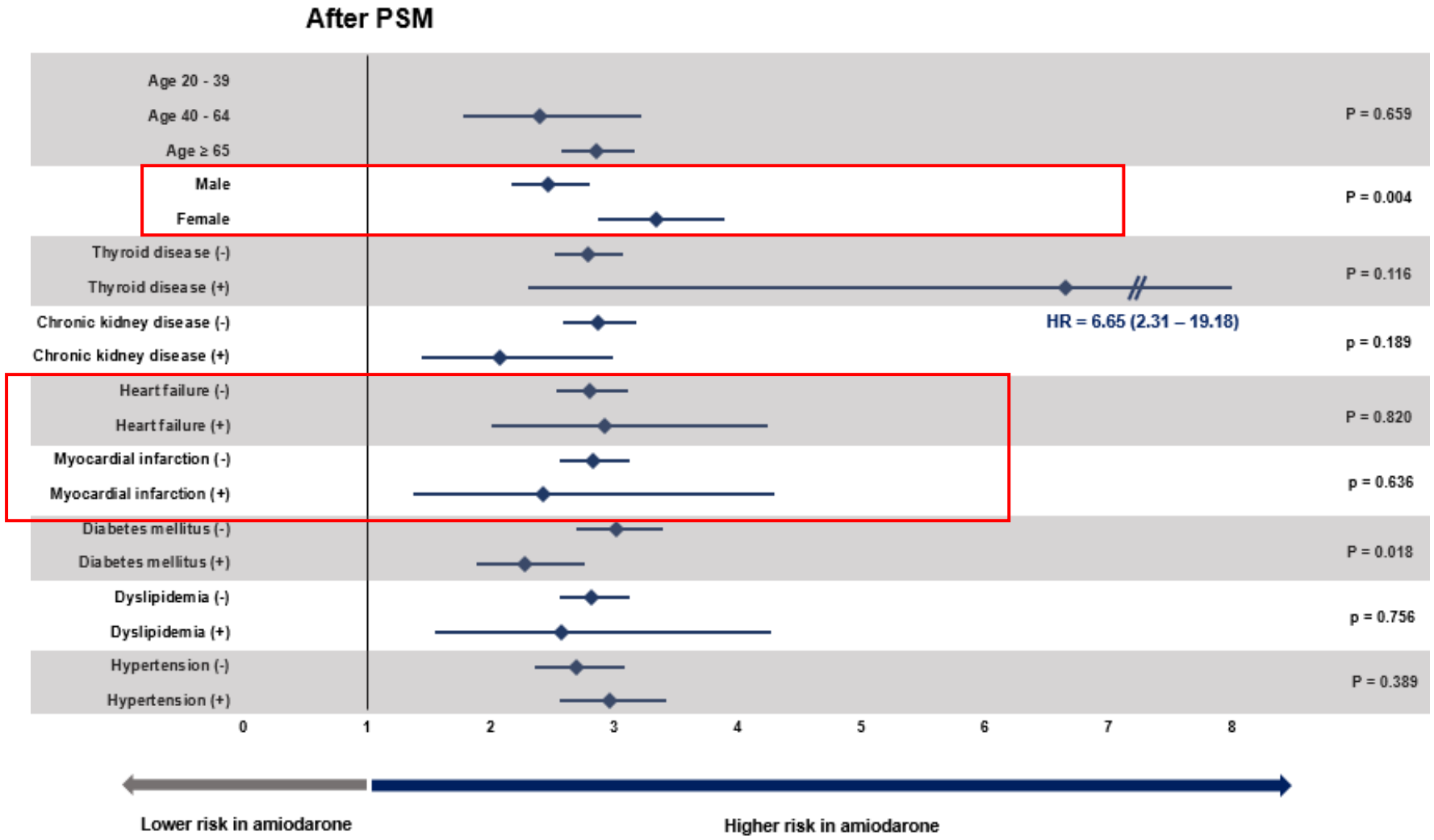


Discussion

The current study demonstrated that

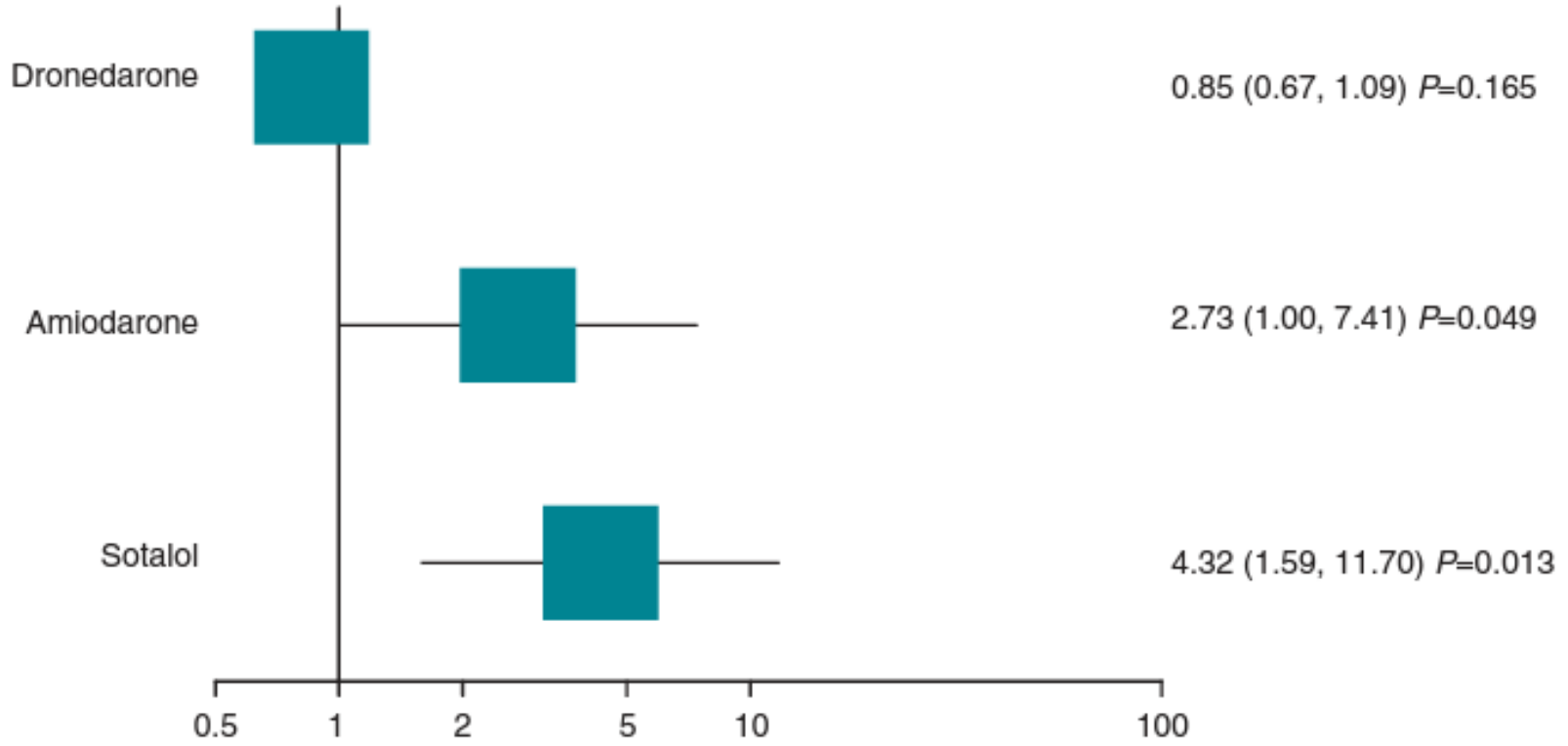
- **Amiodarone use** associated with a significant **increase in overall mortality**
- **Women** were more **vulnerable to amiodarone** use
- **Heart failure and myocardial infarction** showed **no significant interaction with amiodarone** use

Discussion

The explanations for increased mortality associated with amiodarone use

- Systemic adverse effects
- Drug-drug interactions with non-vitamin K oral anticoagulant (NOAC)
- Selection bias

Discussion



Nick Freemantle et el. *Europace* 2011;13:329-345

Discussion

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%[SmPC]	No PK data[a]	+40%[521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[524]	No effect[523]	No effect[525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40%[526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85%[b 523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77%[523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR)[523] (no dose reduction required by label)	+40%[527] (probably not relevant)[528]

Steffel J et el. *EP Europace*. 2021;23:1612-1676

Conclusion

- **Amiodarone**, compared with non-amiodarone AADs, was associated with significantly **increased risk of all-cause mortality** in AAD naive new-onset AF patients.

- **Increased all-cause mortality** associated with amiodarone **was consistent** throughout various subgroups including patients with **prior heart failure and myocardial infarction**.

Thank you