



Mortality of newly diagnosed heart failure treated with amiodarone A propensity-matched study

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ABSTRACT

Background: Studies on the safety of amiodarone therapy in heart failure (HF) presented conflicting results. We evaluated the relationship of commencing treatment with amiodarone (CTA) with the mortality and the morbidity of patients newly diagnosed with HF.

Methods: Prospective cohort study over 7 years on 3734 patients with HF. Main outcomes were all-cause and cardiovascular mortality, hospitalizations and visits. 739 patients who commenced treatment with amiodarone were propensity-matched with another 739 patients. Non-commencing treatment with amiodarone. We analyze the independent relationship of commencing treatment with amiodarone, with the mortality and the morbidity, stratifying patients for cardiovascular co-morbidity, after propensity score-matching.

Results: During a median follow-up of 46.1 months, 644 (43.6%) died, and 1086 (73.5%) were hospitalized. Commencing treatment with amiodarone was associated with a higher all-cause mortality (HR 1.70 [CI 95%, 1.50 to 1.91]), particularly among women (HR: 1.77 [1.55 to 2.00]), and among patients with non-systolic HF (HR: 1.87 [1.66 to 2.09], $P < 0.001$ in all the cases), even after adjustment for the propensity to take amiodarone, or other medications, and other potential confounders. Commencing treatment with amiodarone was not associated with cardiovascular mortality, hospitalizations, or visits.

Conclusion: The commencement of treatment with amiodarone is associated with an increased mortality of patients with heart failure, mainly in women and in patients with non-systolic heart failure.

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1. Introduction

Meta-analyses of randomized trials of amiodarone in chronic heart failure (HF) suggested a reduction in the odds of all-cause mortality associated with amiodarone treatment [1,2]. Guidelines recommend amiodarone as a first-line agent for atrial fibrillation in patients with HF [3]. Nevertheless, studies on the safety of amiodarone in HF presented conflicting results [4–6].

Some antiarrhythmic medications studied in clinical trials of patients with ischemic left-ventricular dysfunction have been shown to increase the risk of death [7–9]. The results of the SCD-HeFT trial [4], the COMET [5], and the VALIANT [6] studies confirming an increased mortality among patients with HF treated with amiodarone, as well as the discontinuation of the ANDROMEDA trial [10] owing to greater mortality associated with use of dronedarone, a non-iodinated derivative of amiodarone, in patients affected by left ventricular dysfunction, have raised concern. Our aim was to evaluate

the effect of amiodarone on mortality and morbidity among patients with HF treated with a contemporary medical regimen.

2. Methods

2.1. Study design and patients

Prospective study of a cohort of patients diagnosed for the first time with HF (3734 patients) during a period of 7 years (1 January 2001 to 31 December 2007). The patients included are residents of a community of 87,106 inhabitants in the south of Spain, served by the University Hospital of Puerto Real (HUPR), Cadiz. The cohort comprises adults (≥ 14 years) diagnosed with HF, according to the Framingham criteria [11]. Diagnosis was made either by consultation between internists and family doctors (3174 patients) or after admission to the hospital (560 patients). The system organized for consultation between internists and family doctors (CIMF) has been described previously [12]. Patients aged less than 14 years and those not permanently resident in the community of reference have been excluded. This study has been undertaken with the approval of the Committee for Ethics and Research of the University Hospital of Puerto Real.

During a median follow-up of 46.1 $\pm$ 11.2 months, 1628 patients (43.6%) died, 2744 (73.5%) were hospitalized for worsening heart failure, and 806 patients (22.1%) commenced treatment with amiodarone. After we excluded patients lost to follow-up ($n = 18$), there were 788 patients who commenced treatment with amiodarone. We matched 739 (95.8%) of the 788 patients who commenced treatment with amiodarone,

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Table 1

Demographic and clinical characteristics of patients diagnosed with heart failure.

	Before propensity-matching			After propensity-matching		
	Amiodarone therapy (n = 826)	Non-amiodarone therapy (n = 2908)	P value	Amiodarone therapy (n = 739)	Non-amiodarone therapy (n = 739)	P value
Age, (mean $\pm$ SD), years	70.7 $\pm$ 7.6	72.1 $\pm$ 8.3	<.01	70.5 $\pm$ 7.3	70.8 $\pm$ 7.8	>.364
Women	72.2 $\pm$ 6.1	74.3 $\pm$ 7.8		72.0 $\pm$ 6.0	71.8 $\pm$ 6.3	
Men	69.3 $\pm$ 7.5	71.6 $\pm$ 8.7		69.5 $\pm$ 7.3	69.2 $\pm$ 7.6	
Women, No. (%)	423 (51.2)	1556 (53.5)	<.01	387 (52.4)	387 (52.4)	>.999
Type of heart failure, No. (%)			<.01			>.645
HF-PSF (LVEF > 50%)	1624 (43.5)	1445 (49.7)		323 (43.7)	320 (43.3)	
HF-DSF (LVEF $\leq$ 50%)	2110 (56.5)	1463 (50.3)		416 (56.3)	419 (56.7)	
Etiology of the HF, No. (%)			<.05			>.172
Ischemic (Angina or AMI)	430 (52.0)	1439 (49.5)		376 (50.9)	219 (51.0)	
Arterial hypertension	351 (42.5)	1181 (40.6)		310 (41.9)	311 (42.1)	
Valvular	63 (7.6)	253 (8.7)		59 (8.0)	60 (8.1)	
Other	40 (4.8)	113 (3.9)		33 (4.5)	32 (4.3)	
Ischemic + Arterial hypertension	231 (28.0)	849 (29.2)		211 (28.6)	210 (28.4)	
Clinical signs, No. (%)			<.05			>.246
Vascular congestion	349 (42.2)	1262 (43.4)		318 (43.0)	317 (42.9)	
Rales	386 (46.7)	1291 (44.4)		339 (45.9)	340 (46.0)	
NYHA functional class I	157 (19.0)	579 (19.9)		142 (19.2)	141 (19.1)	
NYHA functional class II	357 (43.2)	1294 (44.5)		325 (44.0)	325 (44.0)	
NYHA functional class III	226 (27.4)	832 (28.6)		206 (27.9)	207 (28.0)	
NYHA functional class IV	336 (10.4)	204 (7.0)		66 (8.9)	66 (8.9)	
Radiological signs, No. (%)			<.05			>.361
Cardiomegaly	300 (36.3)	1018 (35.0)		264 (35.7)	265 (35.9)	
Interstitial edema	254 (30.8)	858 (29.5)		222 (30.0)	223 (30.2)	
Alveolar edema	247 (29.9)	808 (27.8)		213 (28.8)	214 (29.0)	
Pleural effusion	259 (31.3)	861 (29.6)		228 (30.8)	277 (30.7)	
EKG, No. (%)			<.05			>.832
Sinus rhythm	413 (50.0)	1669 (57.4)		406 (54.9)	407 (55.1)	
Auricular fibrillation/flutter	640 (77.5)	2056 (70.7)		549 (74.0)	545 (73.8)	
Pacemaker rhythm	80 (9.7)	218 (7.5)		58 (7.9)	59 (8.0)	
Pathological Q waves	260 (31.5)	774 (26.6)		212 (28.7)	211 (28.6)	
Left bundle branch block	145 (17.6)	343 (11.8)		96 (13.0)	97 (13.1)	
Comorbidity, No. (%)			<.05			>.746
Angina	242 (29.3)	788 (27.1)		208 (28.1)	208 (28.1)	
AMI	260 (31.5)	806 (27.7)		213 (29.8)	214 (29.0)	
Coronary intervention	218 (26.4)	654 (22.5)		178 (24.1)	177 (24.0)	
CVA/TIA	50 (6.0)	154 (5.3)		43 (5.8)	44 (6.0)	
Peripheral ischemia	108 (13.1)	297 (10.2)		88 (11.9)	87 (11.8)	
Diabetes mellitus	294 (35.6)	933 (32.1)		244 (33.0)	243 (32.9)	
Diabetes mellitus (insulin treatment)	117 (14.2)	314 (10.8)		89 (12.0)	89 (12.0)	
Arterial hypertension	394 (47.7)	1294 (44.5)		339 (45.9)	340 (46.0)	
Left ventricular hypertrophy	275 (33.3)	808 (27.8)		228 (30.8)	229 (31.0)	
Dyslipemia	322 (39.0)	1067 (36.7)		281 (38.0)	280 (37.9)	
LDL > 130 mg/dL	239 (29.0)	904 (31.1)		222 (30.0)	222 (30.0)	
LDL > 100 mg/dL	177 (21.4)	553 (19.0)		149 (20.2)	150 (20.3)	
Smokers	267 (32.3)	820 (28.2)		221 (29.9)	221 (29.9)	
BMI > 30 Kg/m ²	318 (38.5)	1056 (36.3)		274 (37.1)	275 (37.2)	
BMI > 18 Kg/m ²	59 (7.1)	163 (5.6)		46 (6.2)	47 (6.4)	
COPD	162 (19.2)	430 (14.8)		130 (17.6)	130 (17.6)	
Chronic renal failure (Cr > 1.5 mg/dL)	140 (17.0)	433 (14.9)		119 (16.1)	120 (16.2)	
Chronic liver disease	32 (3.9)	87 (3.0)		27 (3.7)	26 (3.5)	
Dementia	26 (3.2)	76 (2.6)		21 (2.8)	20 (2.7)	
Anemia	190 (23.0)	532 (18.3)		154 (20.8)	153 (20.7)	
Women (H2b < 12 mg/dL)	111 (13.4)	268 (9.3)		82 (11.1)	80 (10.8)	
Men (H2b < 13 mg/dL)	88 (10.6)	244 (8.4)		73 (9.9)	74 (10.0)	
Hemoglobin < 10 g/dL	70 (8.5)	192 (6.6)		54 (7.3)	53 (7.2)	
Na < 135 mEq/L	55 (6.7)	128 (4.4)		38 (5.1)	37 (5.0)	
Systemic malignancy	83 (10.1)	378 (11.3)		80 (10.8)	80 (10.8)	
Hyperthyroidism	29 (3.5)	58 (2.0)		20 (2.7)	22 (3.0)	
Hypothyroidism	92 (11.1)	297 (10.2)		79 (10.7)	75 (10.1)	
> 2 Comorbidities, No. (%)	628 (76.0)	2070 (71.2)	.0125	551 (74.6)	549 (74.3)	>.895
Women	347 (42.0)	1041 (35.8)		288 (39.0)	288 (39.0)	
Men	306 (37.1)	977 (33.6)		259 (35.0)	259 (35.0)	
Charlson Index, (mean $\pm$ SD)	3.3 $\pm$ 1.1	2.2 $\pm$ 1.1	.0143	2.7 $\pm$ 1.2	2.8 $\pm$ 1.1	>.874
Echocardiographic data, (mean $\pm$ SD)						
LVEDD, mm	52.7 $\pm$ 2.2	51.0 $\pm$ 2.0	=.003	52.3 $\pm$ 2.3	52.1 $\pm$ 2.0	=.553
Septum, mm	12.3 $\pm$ 0.4	11.1 $\pm$ 0.2	=.023	12.0 $\pm$ 0.4	11.9 $\pm$ 0.3	=.879
Posterior wall, mm	12.0 $\pm$ 0.3	10.9 $\pm$ 0.2	<.005	11.9 $\pm$ 0.3	11.2 $\pm$ 0.2	=.062
LA, parasternal, mm	43.1 $\pm$ 2.0	42.2 $\pm$ 2.0	=.026	42.7 $\pm$ 2.3	42.5 $\pm$ 1.4	=.547
LVMI, g/m ²	130.7 $\pm$ 6.8	129.0 $\pm$ 6.1	=.008	130.0 $\pm$ 6.5	129.6 $\pm$ 6.2	=.081
Diastolic wall stress, kdyn/cm ²	18.7 $\pm$ 1.0	17.4 $\pm$ 0.8	=.019	18.2 $\pm$ 1.1	18.0 $\pm$ 0.9	=.498
Mitral flow E/A	0.98 $\pm$ 0.02	0.99 $\pm$ 0.02	=.093	0.99 $\pm$ 0.03	0.98 $\pm$ 0.02	>.975

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