

Dronedarona. De la evidencia a la práctica clínica.

Dr. Antonio Esteban
Unidad de Estimulación Cardíaca.
Servicio de Cardiología.
Hospital Costa del Sol Marbella

A poster for the 50th Congress of the Andalusian Society of Cardiology. The background is a dark blue sky with a view of the Alhambra in Granada at dusk. The text is in white and yellow. In the top left corner, there are logos for the Spanish Society of Cardiology (SEAC) and the Andalusian Society of Cardiology (SEAC). In the top right corner, the website URL "INFO@CONGRESOANDALUZ.COM" and "WWW.CONGRESOANDALUZ.COM" is displayed. The main text reads: "50 CONGRESO SOCIEDAD ANDALUZA DE CARDIOLOGÍA 'CONGRESO ANDALUZ DE LAS ENFERMEDADES CARDIOVASCULARES'". Below this, the dates "14 - 16 MAYO 2015" and the location "HOTEL ABADES NEVADA PALACE - GRANADA" are listed. In the bottom right corner, there is a logo for "Fase20" and contact information for the organizing committee.

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CONGRESO SOCIEDAD
ANDALUZA DE CARDIOLOGÍA
"CONGRESO ANDALUZ
DE LAS ENFERMEDADES
CARDIOVASCULARES"

14 - 16 MAYO 2015
HOTEL ABADES NEVADA PALACE - GRANADA

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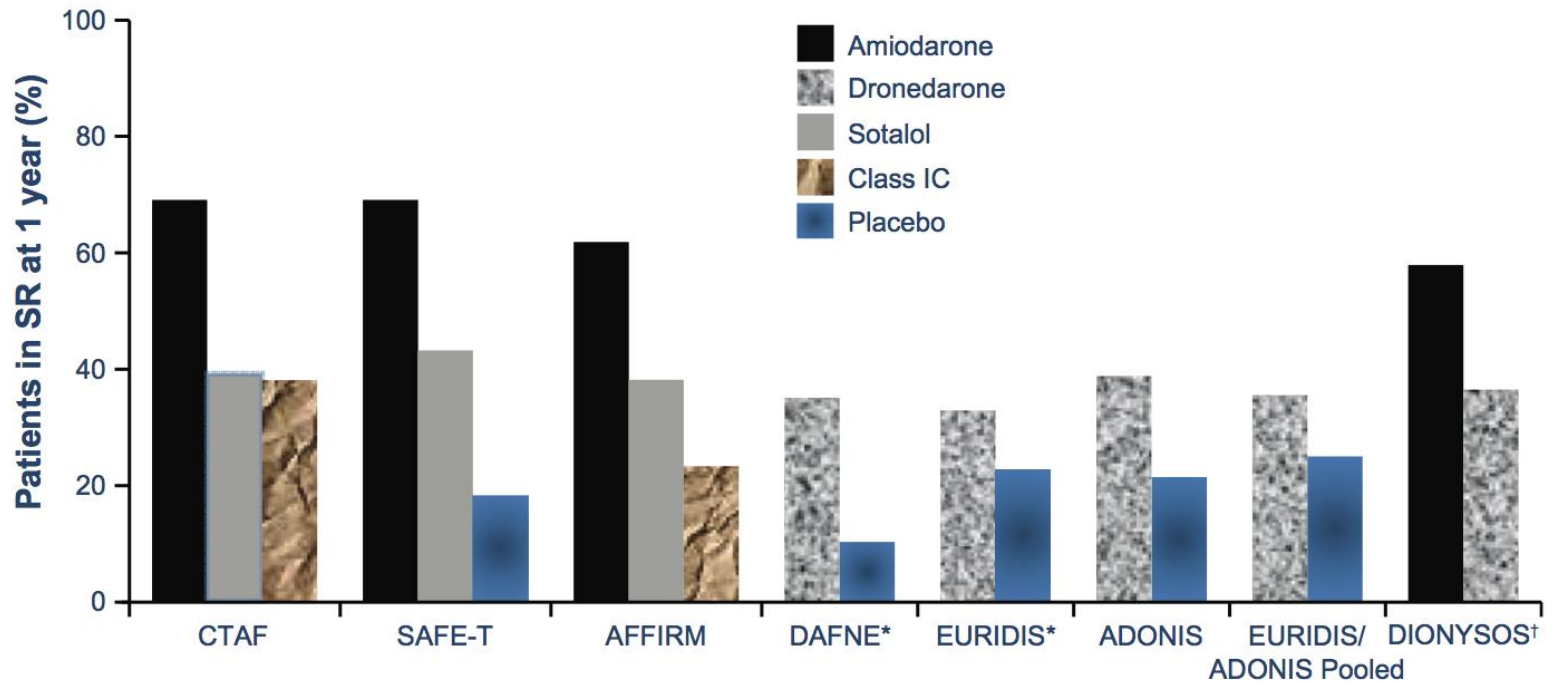


Figure 6. Comparative efficacy of antiarrhythmic drugs including dronedarone in maintaining sinus rhythm in placebo-controlled or active-controlled trials.

¿ CUAL IRÁ PEOR ...?



Dronedarona: El FAA más estudiado para tratar la FA

10.676 pacientes. 5.553 en dronedarona

Estudios	n	Población	Objetivos
Control del ritmo y de la frecuencia			
DAFNE ¹	270	FA persistente	Búsqueda de dosis: cardioversión y mantenimiento del ritmo sinusal
EURIDIS ²	612	FA paroxística/persistente	Mantenimiento del ritmo sinusal
ADONIS ²	625	FA paroxística/persistente	Mantenimiento del ritmo sinusal
ERATO ³	174	FA permanente	Control de la frecuencia ventricular
DIONYSOS ⁴	504	FA persistente	Ensayo comparativo frente a amiodarona
ICC recientemente descompensada			
ANDROMEDA ⁵	627/1000*	ICC inestable y disfunción VI (FA 25%)	Estudio de morbi-mortalidad con ICC
eventos clínicos			
ATHENA ⁶	4628	FA paroxística/persistente	Prevención de hospitalización cardiovascular o muerte por cualquier causa
PALLAS ⁷	3149/10 800*	FA permanente	Prevención de eventos CV importantes y de hospitalización por causa CV o muerte por cualquier causa

Mantenimiento del ritmo sinusal

ESTUDIOS EURIDIS Y ADONIS



Am Heart J 2008;156:527.e1-527.e9.

Estudio de intervalo de dosis

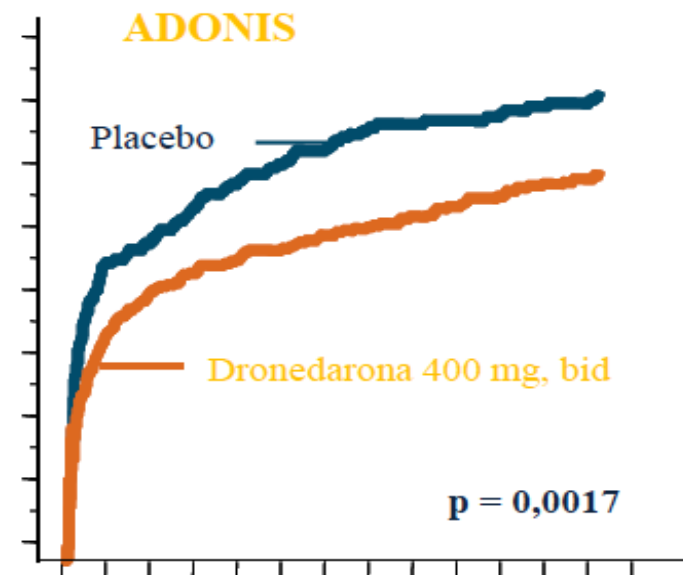
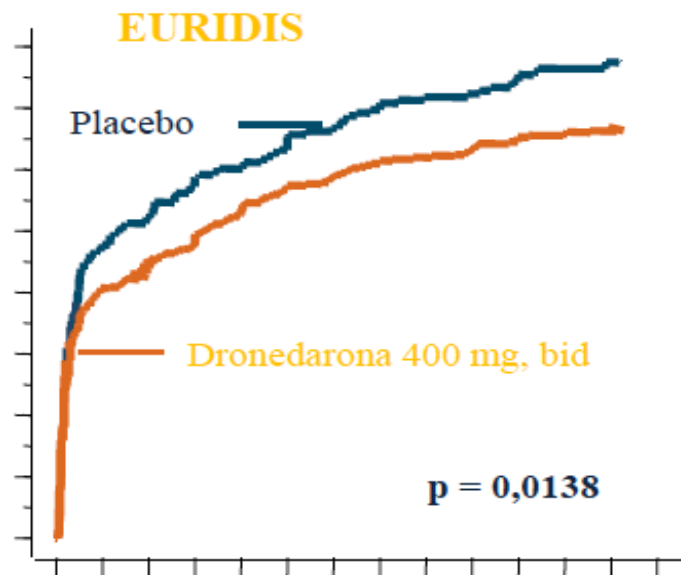
ESTUDIO DAFNE



European Heart Journal (2003) 24, 1481-1487

Dronedarona: derivado de amiodarona no yodado y menos lipofílico

- Propiedades electrofisiológicas similares.
- Prolonga el tiempo hasta la primera recurrencia (DAFNE, ADONIS, EURIDIS).
- Semivida: 24 h.
- No se ha descrito toxicidad orgánica (tiroidea, pulmonar) o proarritmia.
- Dosis: 400 mg/12 h.



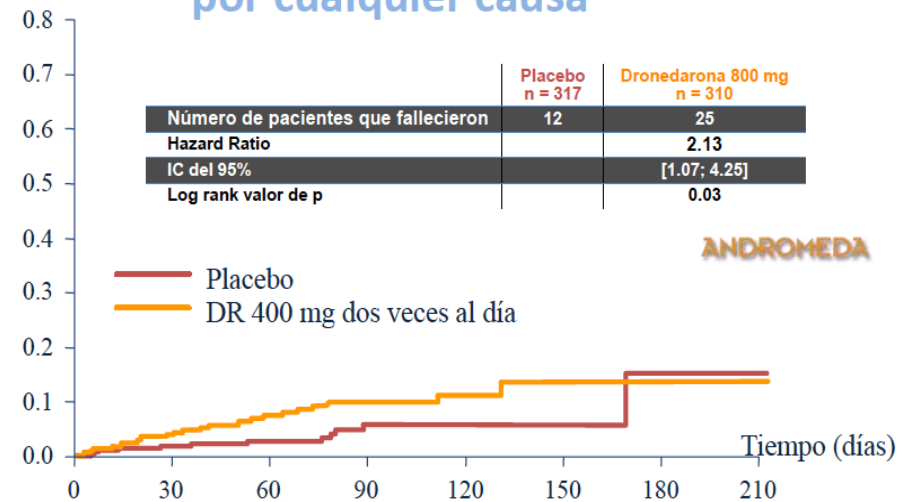
Estudio ANDROMEDA.



Criterios de inclusión

- ▶ **Pacientes hospitalizados consecutivos**
- ▶ **Edad ≥ 18 años**
- ▶ **Presencia o sospecha de ICC sintomática (clase II-IV según la NYHA) con**
- ▶ **Al menos un episodio de descompensación de clase III-IV según la NYHA en el último mes**
- ▶ **Tratados con un diurético**
- ▶ **IMP $\leq 1,2$ ~ FEVI $\leq 0,35$**
- ▶ **Consentimiento informado firmado**

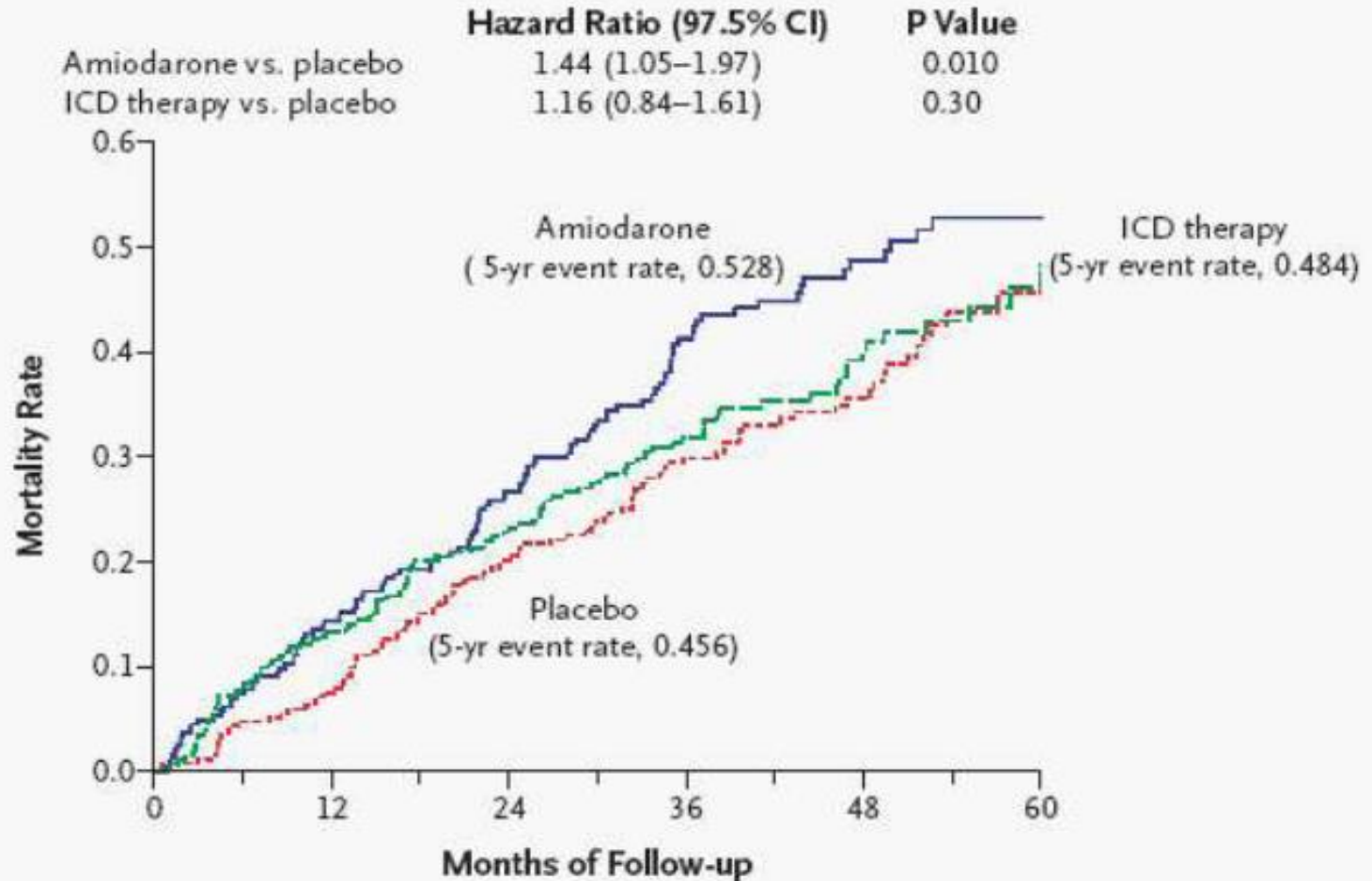
Incidencia acumulada de muerte por cualquier causa



Pacientes en riesgo:

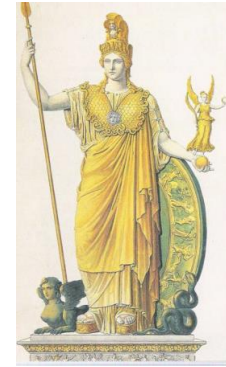
	0	30	60	90	120	150	180	210
Placebo	317	256	181	103	50	18	6	1
DR 400 mg dos veces al día	310	257	174	104	59	22	5	1

SCD-HEFT Trial... El Andr6meda de la Amiodarona



No. at Risk						
Amiodarone	244	209	179	106	58	21
Placebo	253	234	202	138	86	17
ICD therapy	263	228	202	130	68	23

Estudio ATHENA.

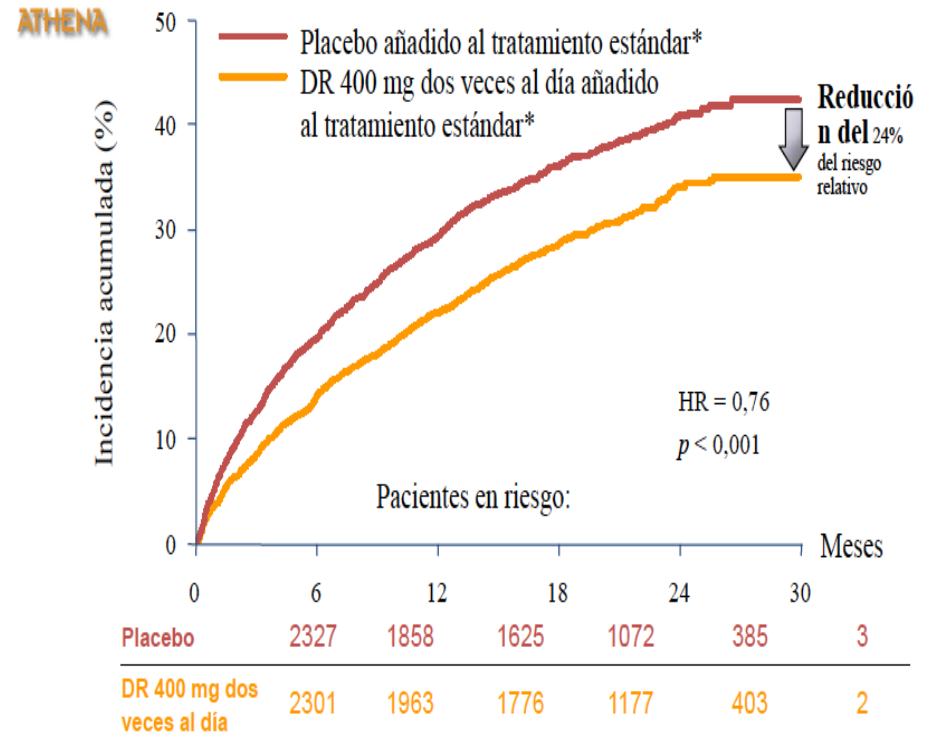


Criterios de inclusión

- ▶ **Pacientes de alto riesgo con antecedentes de FA/FIA paroxística o persistente**
- ▶ **Edad ≥ 75 años con o sin factores de riesgo adicionales**
- ▶ **Edad ≥ 70 años y ≥ 1 factor de riesgo (hipertensión arterial, diabetes, ACV/AIT previo, AI ≥ 50 mm, FEVI $< 0,40$)**

- ▶ **Originalmente, el protocolo permitía la inclusión en el estudio de pacientes < 70 años de edad con factores de riesgo adicionales**
- ▶ **El protocolo se modificó posteriormente para incluir solamente a pacientes ≥ 70 años de edad**

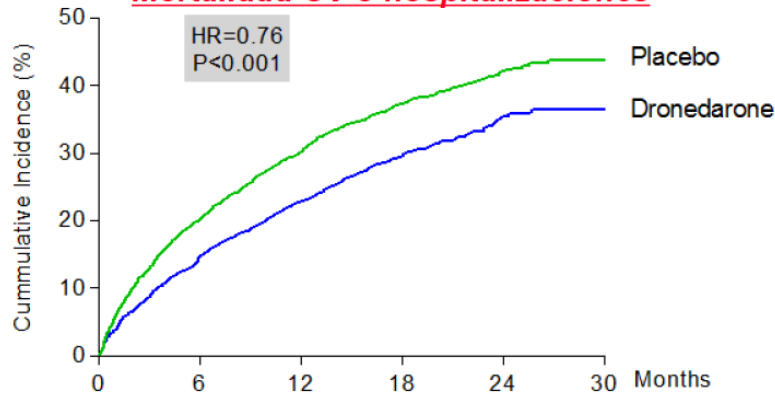
Dronedarona disminuyó significativamente el riesgo de muerte u hospitalización por causas CV en un 24%



Estudio ATHENA.

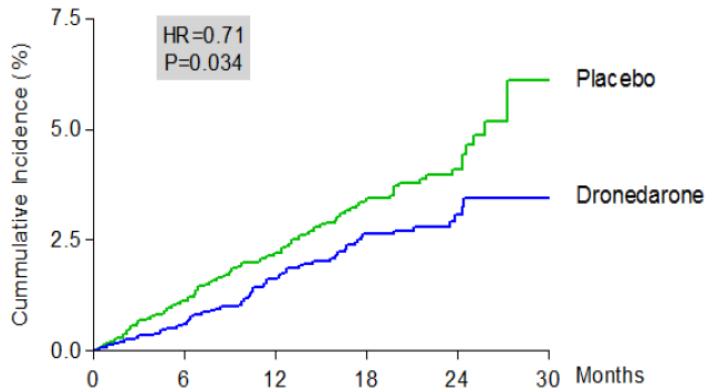


Mortalidad CV o hospitalizaciones



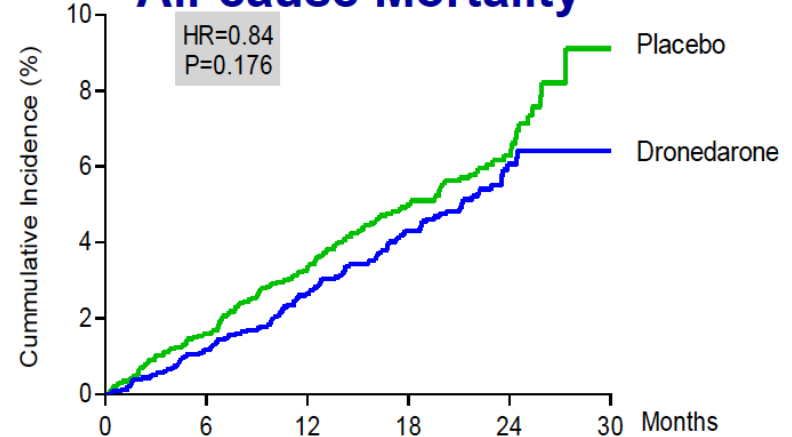
Time (Months)	0	6	12	18	24	30
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

CV Mortality



Time (Months)	0	6	12	18	24	30
Placebo	2327	2290	2250	1629	636	7
Dronedarone	2301	2274	2240	1593	615	4

All-cause Mortality

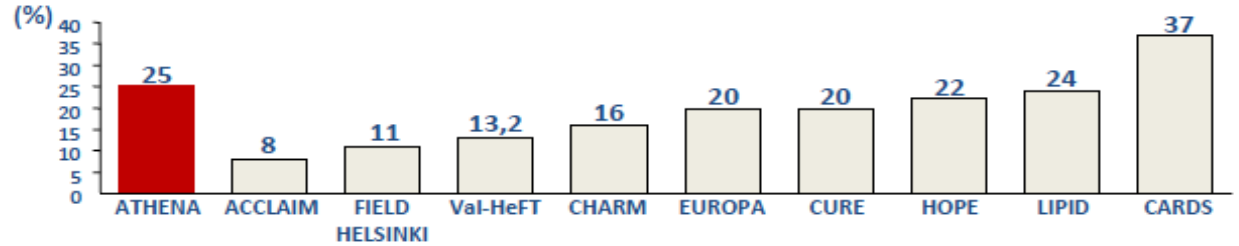


Time (Months)	0	6	12	18	24	30
Placebo	2327	2290	2250	1629	636	7
Dronedarone	2301	2274	2240	1593	615	4

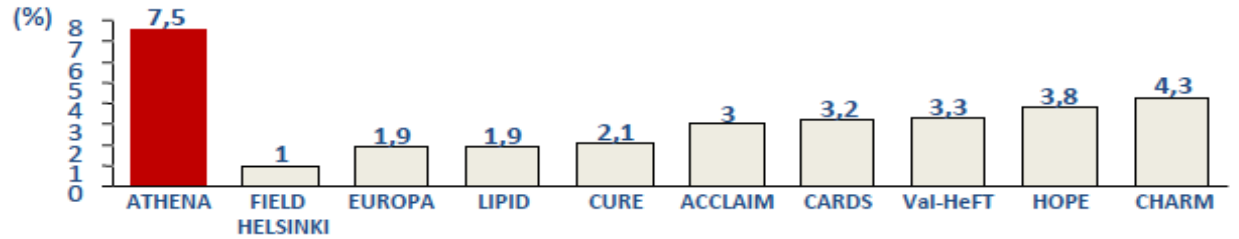
Ensayos con eventos de morbi-mortalidad CV

**Morbi-
Mortality
annualized**

Relative
Risk
Reduction

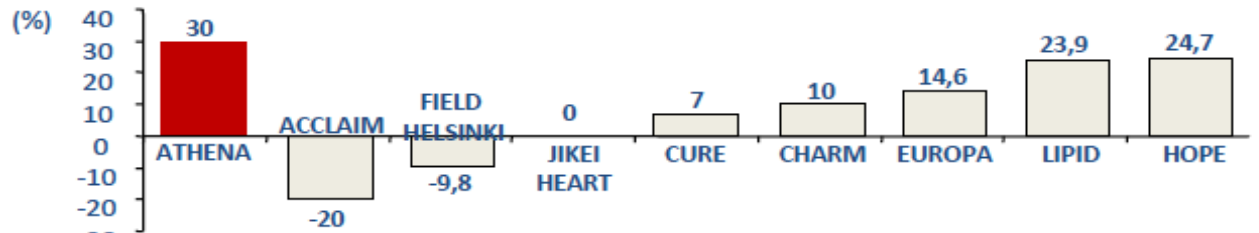


Absolute
Risk
Reduction

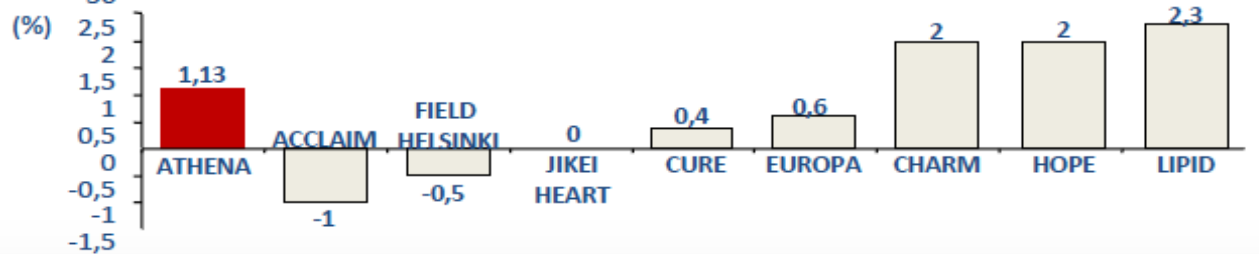


**CV
Mortality
annualized**

Relative
Risk
Reduction



Absolute
Risk
Reduction



ORIGINAL ARTICLE

Dronedarone in High-Risk Permanent Atrial Fibrillation

Stuart J. Connolly, M.D., A. John Camm, M.D., Jonathan L. Halperin, M.D., Campbell Joyner, M.D., Marco Alings, M.D., John Amerena, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Per Blomström, M.D., Martin Borggrefe, M.D., Andrzej Budaj, M.D., Shih-Ann Chen, M.D., Chi Keong Ching, M.D., Patrick Commerford, M.D., Antonio Dans, M.D., Jean-Marc Davy, M.D., Etienne Delacrétaiz, M.D., Giuseppe Di Pasquale, M.D., Rafael Diaz, M.D., Paul Dorian, M.D., Greg Flaker, M.D., Sergey Golitsyn, M.D., Antonio Gonzalez-Hermosillo, M.D., Christopher B. Granger, M.D., Hein Heidbüchel, M.D., Josef Kautzner, M.D., June Soo Kim, M.D., Fernando Lanas, M.D., Basil S. Lewis, M.D., Jose L. Merino, M.D., Carlos Morillo, M.D., Jan Murin, M.D., Calambur Narasimhan, M.D., Ernesto Paolasso, M.D., Alexander Parkhomenko, M.D., Nicholas S. Peters, M.D., Kui-Hian Sim, M.D., Martin K. Stiles, M.D., Supachai Tanomsup, M.D., Lauri Toivonen, M.D., János Tomcsányi, M.D., Christian Torp-Pedersen, M.D., Hung-Fat Tse, M.D., Panos Vardas, M.D., Dragos Vinereanu, M.D., Denis Xavier, M.D., Jun Zhu, M.D., Jun-Ren Zhu, M.D., Lydie Baret-Cormel, M.D., Estelle Weinling, Pharm.D., Christoph Staiger, M.D., Salim Yusuf, M.D., Susan Chrolavicius, R.N., B.A., Rizwan Afzal, M.Sc., and Stefan H. Hohnloser, M.D., for the PALLAS Investigators*

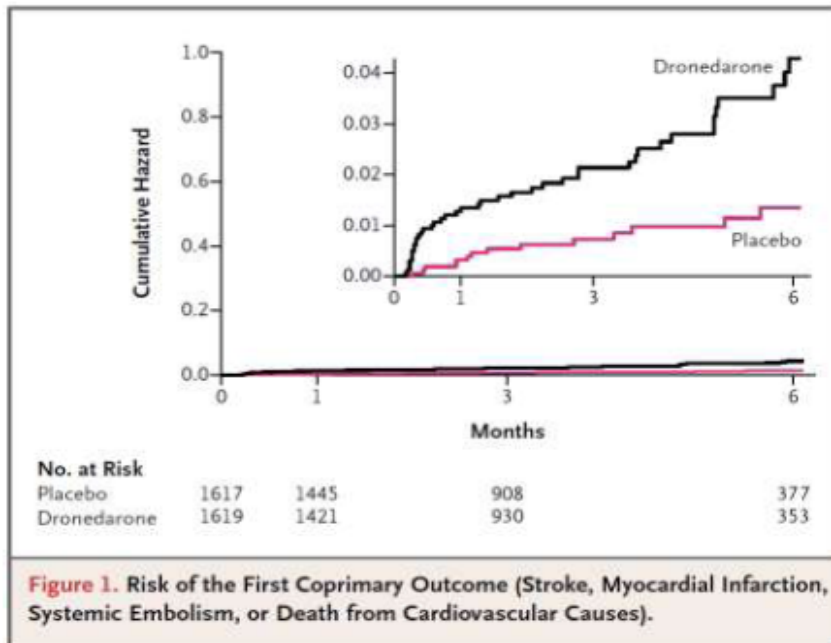
PALLAS: Inclusion criteria

1. Permanent AF
 - > 6 months
(ECG or medical report)
2. ≥ 65 years
3. CV disease
 - CAD, HF, LV EF $\leq 40\%$
 - Stroke
 - Peripheral vascular disease
 - ≥ 75 yo + HT + DBM

Estudio PALLAS.



Dronedarone in High-Risk Permanent Atrial Fibrillation



N Engl J Med 2011;365:2268-76.

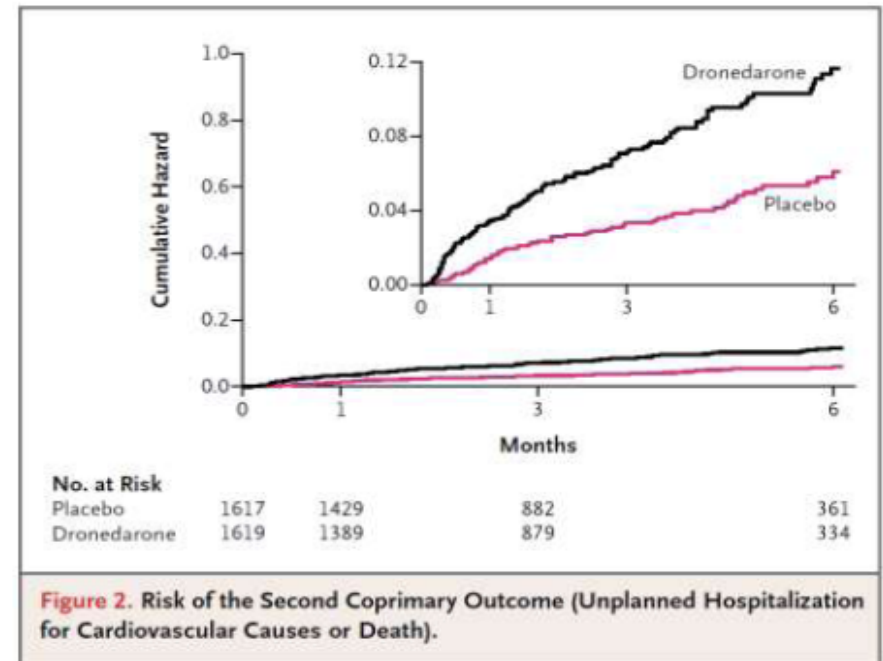


Table 1. A Comparison of Demographic and Clinical Characteristics and Outcomes among Patients in Three Studies of Dronedarone.*

Variable	ATHENA	PALLAS	ANDROMEDA
Demographic characteristic			
Mean age (yr)	72	75	72
Female sex (%)	47	35	25
Clinical characteristic (%)			
Baseline atrial fibrillation	25	100	25
Hypertension	86	83	37
Coronary artery disease	30	41	65
Congestive heart failure class II or III	21	54	97
Treatment (%)			
Beta-blocker	71	74	61
Digoxin	14	33	31
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	70	78	86
Oral anticoagulant	60	84	31
Outcome (hazard ratio) †			
Death			
Any cause	0.84	1.94	2.13
Cardiovascular cause	0.71	2.11	2.75
Presumed arrhythmia	0.55	3.26	1.68
Stroke	0.66	2.32	NA
Congestive heart failure ‡	0.86	1.89	1.22

PACIENTES CON DRONEDARONA

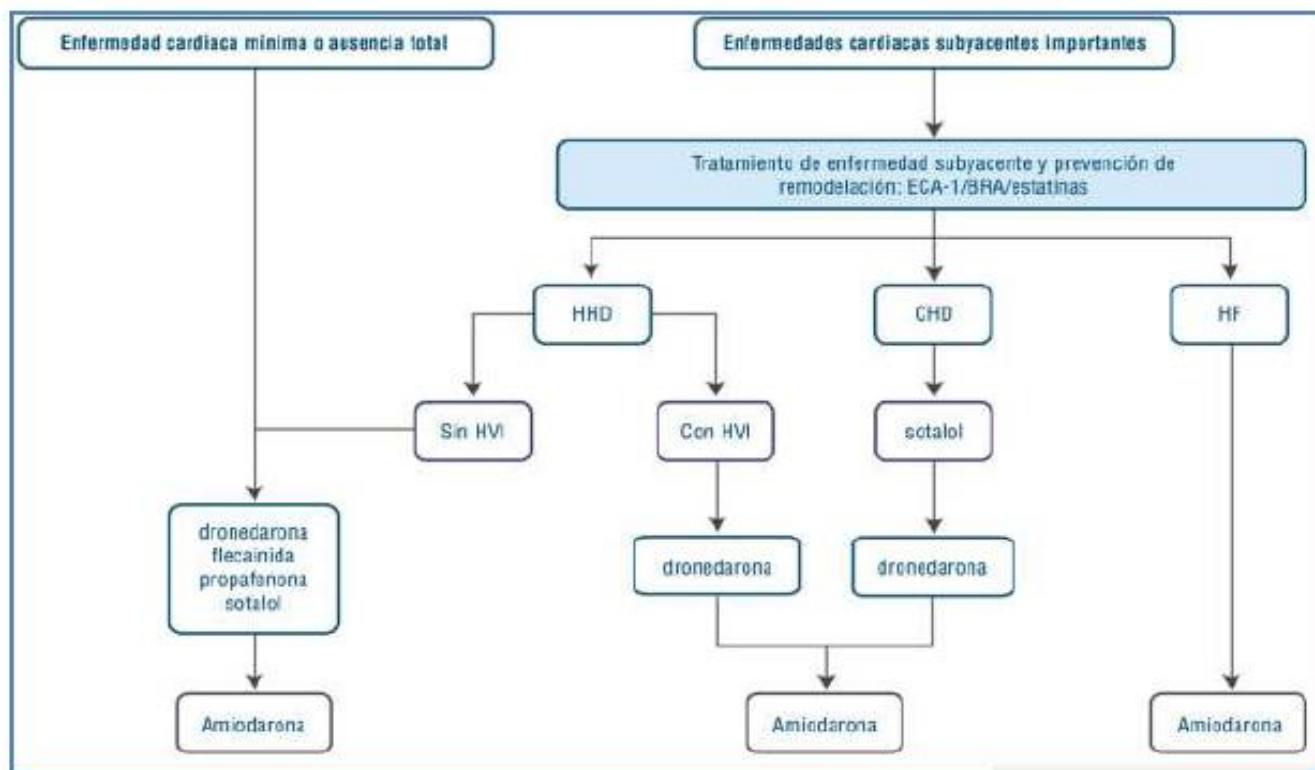
- ↓ 8 lpm
- ↓ 3-4 mmHg PAS
- ↓ 3% el TTR (INR)
- ↑ 6 mm QTc
- ↑ Interrupción del tto (21% vs 11%)
- ↑ 0.3 ng/ml digoxinemia (media 1.2+/-0.8)



Nattel NEJM 2011



Guías de la ESC sobre FA 2012: elección del fármaco antiarrítmico: patología subyacente



- Dronedarona no debe administrarse a pacientes con disfunción sistólica ventricular izquierda o pacientes con episodios previos o en curso de insuficiencia cardíaca. Debe hacerse un seguimiento de los pacientes ante un posible desarrollo de la disfunción sistólica ventricular izquierda durante el tratamiento. Si se desarrolla disfunción sistólica ventricular izquierda, debe interrumpirse el tratamiento con Dronedarona.
- Dronedarona debe utilizarse con precaución en pacientes con cardiopatía isquémica.

CONTROL DEL RITMO: MANTENIMIENTO DEL RITMO SINUSAL

TRATAMIENTO DE CONDICIONES ASOCIADAS
Valorar TTO β -Bloqueantes y Prevención del remodelado
PROFILAXIS TROMBOEMBÓLICA

¿CARDIOPATÍA SIGNIFICATIVA?

NO (o HTA con HVI LEVE-MODERADA)

SI 1º: TTO de la CARDIOPATIA

Flecainida
Propafenona
Dronedaron
Sotanol

HTA
(HVI > 1,4)

Dronedaron

Cardiopatía
isquémica

Dronedaron
Sotanol

Insuficiencia cardíaca
Disfunción sistólica VI

Valorar Amiodarona

terapia no farmacológica (Ablación con RF)

Over 1,3 million patients exposed to dronedarone throughout 40 countries up to 31 March 2014*

North America

~826,000 patients

United States
~796,000



Canada
~ 22,000



Germany
~245,000



Spain
~ 70,000



Italy
~ 53,000



France
~ 27,000



United Kingdom
~ 24,000



~1,315,657
patients*

treated since launch

WORLDWIDE

* Cumulative number of patients. Estimated. IMS/MIDAS Worldwide Monthly Database, Standard Units Sold up until 31 March 2014.

Estudios mundo real vs Estudios aleatorizados

	Eficacia (Clinical trial)	Efectividad (Real world data)
Objetivo	Funciona en condiciones ideales?	Funciona en condiciones usuales?
Diseño	Ensayo controlado	Practica en el mundo real
Objetivo	Aprobación regulatoria	Comportamiento del fármaco
Intervención/Tratamiento	Fijo	Flexible
Comparador	Activo	Practica habitual
Población	Homogenea / Muy seleccionada	Heterogenea / cualquiera
Compliance	Alta	Variable
Validez interna	Alta	Baja
Validez externa (generalizable a otras poblaciones)	Baja-Media	Media-Alta



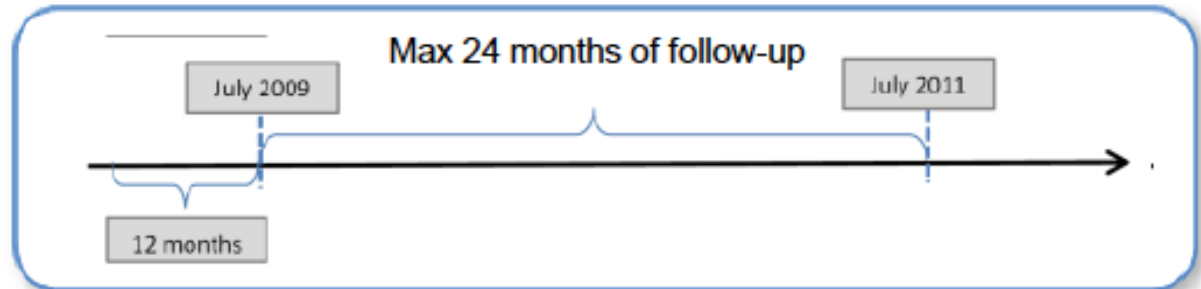
DoD Comparative Effectiveness Study: Objectives

- To compare the effectiveness of dronedarone and current established treatments for AF/AFL, as measured by the occurrence of health outcomes
- Specific objectives associated with the use of either dronedarone or comparators include:
 - Identification of the demographic and clinical characteristics of patients treated for AF/AFL
 - Assessment of health outcomes including
 - Hospitalization of patients for at least 1 night (CV and non-CV)
 - Death (all-cause or CV)

DoD Study Design: Study duration

- Retrospective (historical) cohort

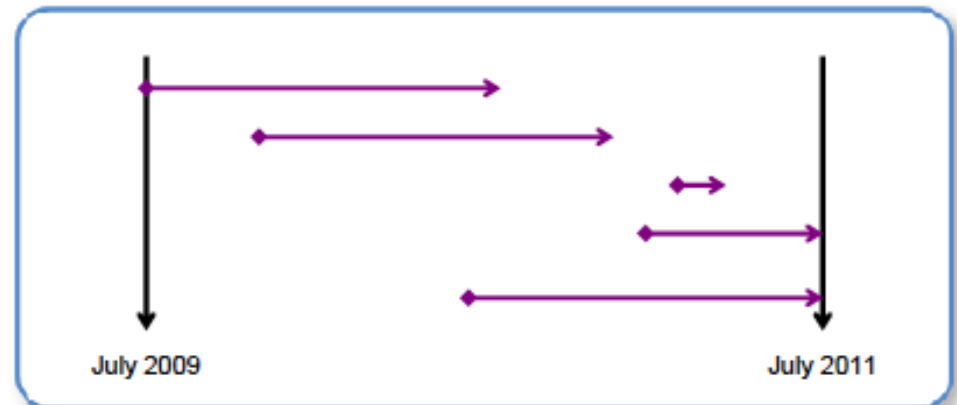
- Study time period:



- Patients censoring process:

- Discontinuation of the index drug (+ 60 days to take into account various half-life)
- Switch or addition of another study drug
- Loss of eligibility for health care in the DoD database
- End of study period (July 2011)
- Death

- Patient's follow-up:



DoD study design: propensity score model variables

- ▶ To control for potential confounding and bias, propensity score (PS) matching used
 - Ratio 1:2 (dronedarone, other AADs respectively)

Demographic variables

- Age*
- Gender (% male)*
- Index date*
- Charlson score*
- AF without other CV disease – Y/N
- COPD – Y/N

History of comorbid conditions – Y/N

- Hypertension*
- Diabetes*
- TIA or stroke*
- Structural heart disease*
- Coronary heart disease*
- Valvular heart disease*
- Non-ischaemic cardiomyopathy
- Congestive heart failure*

History of comorbid procedures – Y/N

- Ablation
- Cardiac surgery*
- Pacemaker evaluation
- Pacemaker insertion*
- Stent placement
- Valve placement*
- Valvular surgery*
- Major open heart surgery*

History of concomitant medication use – Y/N

- ACE inhibitors or ARBs*
- Statins*
- Beta blockers*
- Anticoagulants*
- Warfarin
- Dabigatran*
- Aspirin, prescribed by physician*

Medical encounters

- Hospitalization in prior year – Y/N*
- Number of office visits in prior year
- Skilled nursing facility visit in prior year – Y/N*
- Number of other study medications in prior year – Y/N*
- Number of other nonstudy medications in prior year

Prior event occurrence – Y/N*

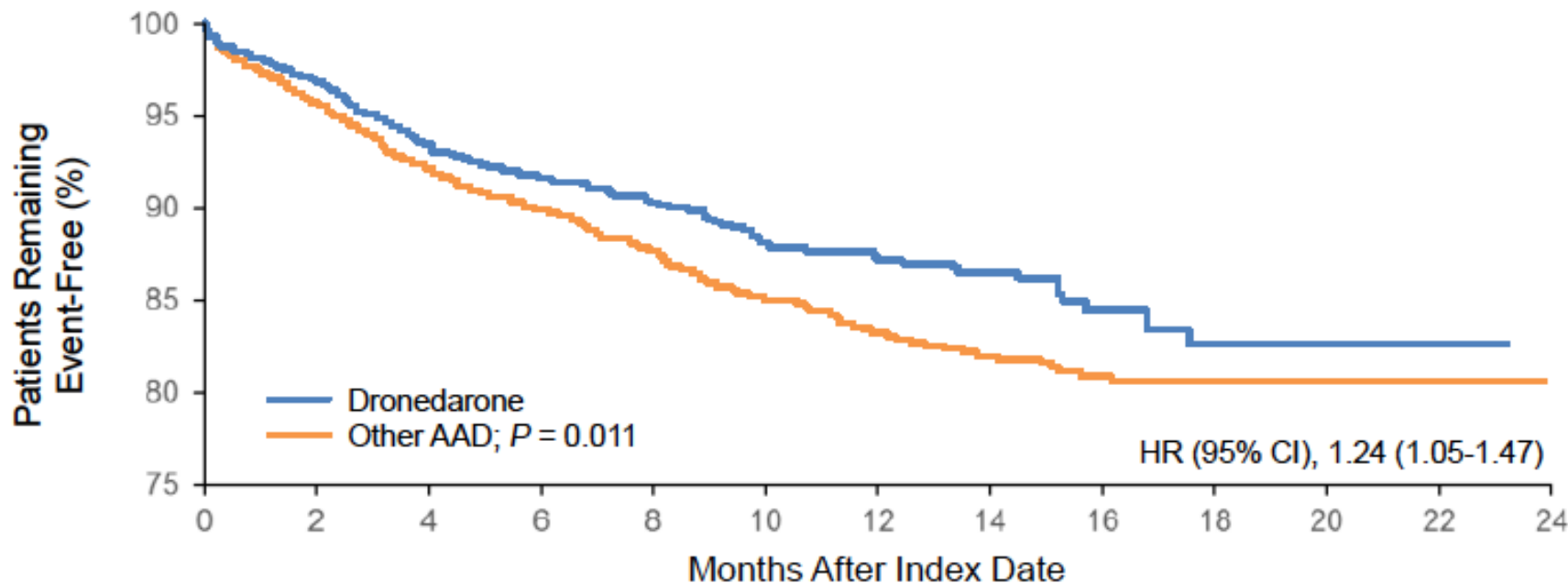
- Prior acute myocardial infarction
- Prior stable angina pectoris
- Prior arrhythmia
- Prior cerebrovascular accident
- Prior deep vein thrombosis
- Prior hospitalized bleeding
- Prior pulmonary embolism
- Prior systemic arterial embolism
- Prior syncope
- Prior stroke

DoD Effectiveness Study

Baseline demography of new initiators post PS matching

	Dronedarone after PS matching	Other AADs after PS matching
All patients, n (%)	2,468 (100.0)	4,936 (100.0)
Mean age (years)	72.1	70.7
Male, n (%)	1,444 (58.5)	2,997 (60.7)
History of disease, n (%)		
AF/AFL	2,468 (100.0)	4,936 (100.0)
AF without CV disease	927 (37.6)	1,812 (36.7)
CV hospitalization	928 (37.6)	1,928 (39.1)
Hypertension	2,038 (82.6)	4,045 (81.9)
Diabetes	733 (29.7)	1,421 (28.8)
TIA/stroke	306 (12.4)	568 (11.5)
Structural heart disease	630 (25.5)	1,360 (27.6)
Coronary heart disease	1,269 (51.4)	2,579 (52.2)
Valvular heart disease	991 (40.2)	1,936 (39.2)
CHF	693 (28.1)	1,328 (26.9)

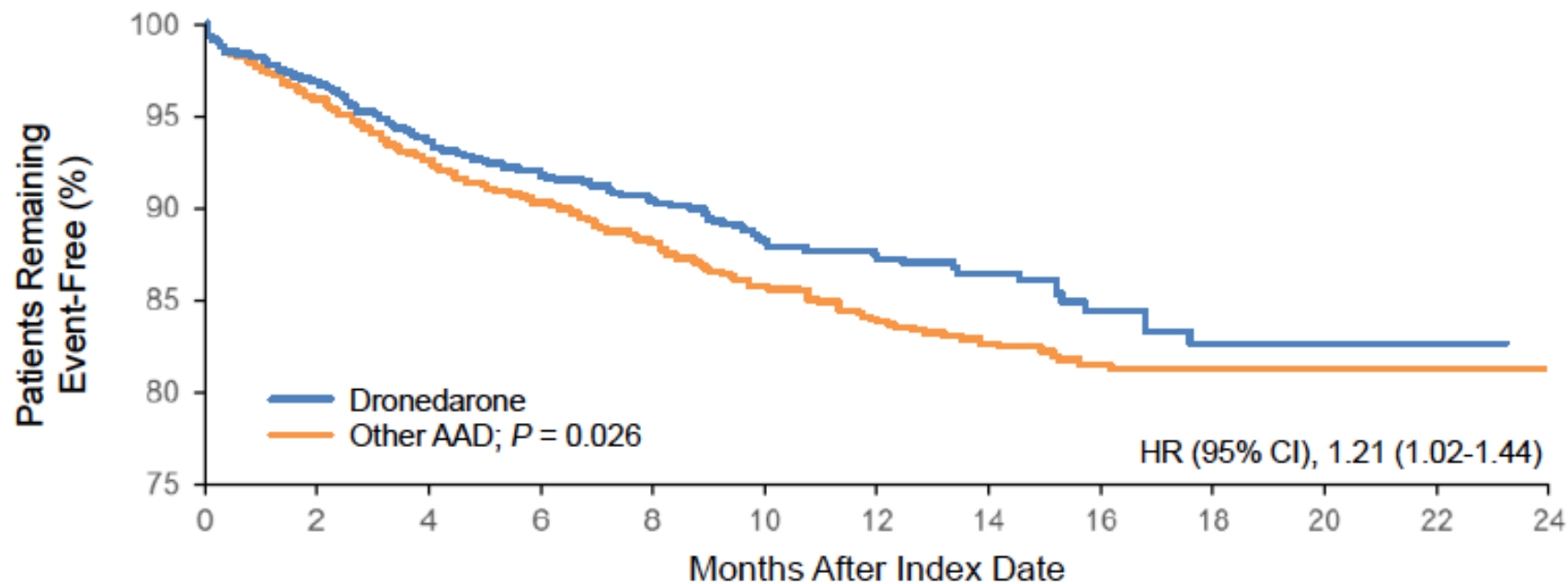
CV hospitalizations and/or death from any cause



Dronedarone:	2468	1875	1309	929	713	523	397	279	171	106	43	11	0
Other AAD:	4936	3818	2305	1587	1132	820	581	428	279	159	98	56	0

Significant increased risk of CV hospitalization and/or death in the “other AADs” cohort compared to dronedarone

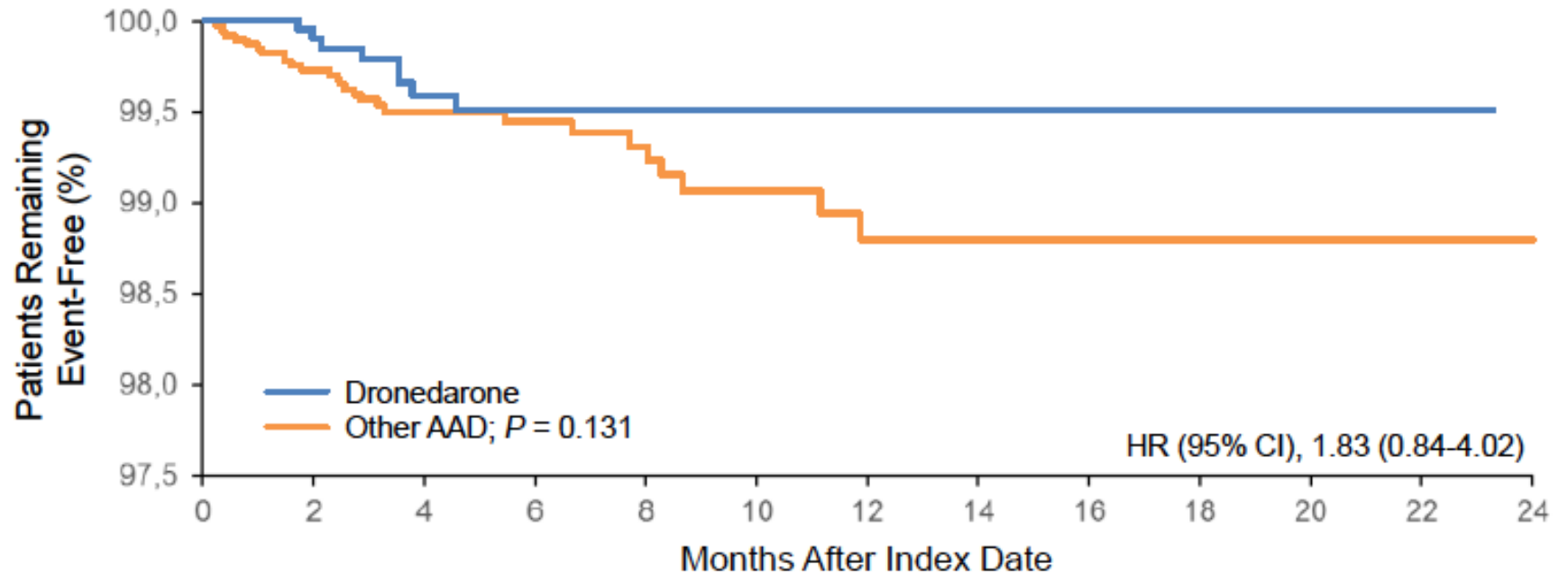
CV hospitalizations



Dronedaron:	2468	1875	1309	929	713	523	397	279	171	106	43	11	0
Other AAD:	4936	3818	2305	1587	1132	820	581	428	279	159	98	56	0

Significant increased risk of CV hospitalization in the “other AADs” cohort compared to dronedaron

All-cause mortality



Dronedarone:	2468	1925	1381	986	761	567	434	301	189	115	50	12	0
Other AAD:	4936	3976	2493	1740	1262	928	663	492	320	184	113	63	0

Dronedarone: non-significant lower all-cause mortality compared with “other AADs”

DoD effectiveness study

Abstract (Boston AF 2014): BAF2014-3004

« Real-life comparison of dronedarone with other antiarrhythmic drugs on cardiovascular outcomes in atrial fibrillation: an updated analysis of a large US population

Table 1: Other AAD Versus Dronedarone on CV Outcomes

Key outcomes (n, %)	Other AAD (N =4936)	Dronedarone (N=2468)	HR [95% CI]	P-value
CV hospitalization and/or death (all-cause)	453 (9.2)	196 (7.9)	1.24 [1.05, 1.47]*	0.011
All-cause mortality	28 (0.6)	8 (0.3)	1.83 [0.84, 4.02]	0.131
CV-related mortality	3 (0.1)	2 (0.1)	0.77 [0.13, 4.61]	0.774
CV hospitalization	429 (8.7)	190 (7.7)	1.21 [1.02, 1.44]	0.026
Non-CV hospitalization	678 (13.7)	286 (11.6)	1.29 [1.12, 1.48]	<0.001
Non-hospitalized cardioversion	596 (12.1)	369 (15.0)	0.81 [0.71, 0.92]	0.001
Hospitalization for arrhythmia	54 (1.1)	14 (0.6)	2.01 [1.11, 3.61]	0.020
Hospitalization for CV surgery	172 (3.5)	68 (2.8)	1.34 [1.02, 1.78]	0.039

* Sensitivity analyses: HR=1.26 [95% CI: 1.01, 1.57]; P=0.037 (ratio 1:1, caliper 0.001) and HR=1.29 [95% CI: 1.05; 1.59]; P=0.012 (ratio 2:1, caliper 0.001).

Conclusions

- ▶ Consistency of CV hospitalization and mortality results between this real-life study and the randomized ATHENA clinical trial:
 - Dronedarone showed significantly lower risk of CV hospitalization and/or death from any cause than “other AADs” and
 - Numerically lower all-cause mortality (not significant)

- ▶ Consistency of rhythm / cardioversion results between this study and the randomized DIONYSOS clinical trial:
 - Dronedarone showed a significantly higher rate of non-hospitalized cardioversion than “other AADs”
 - In the DIONYSOS clinical trial, dronedarone was less effective in the maintenance of normal sinus rhythm than amiodarone

Safety of Dronedarone in Routine Clinical Care



Leif Friberg, MD, PhD

Stockholm, Sweden

- Objectives** The aim of this study was to examine mortality and liver disease among patients exposed to dronedarone.
- Background** There has been concern about the safety of dronedarone, especially for patients with heart failure and permanent atrial fibrillation (AF). There have also been suspicions about liver toxicity.
- Methods** All 174,995 patients with a diagnosis of AF during 2010 to 2012 were identified in the Swedish Patient Register. Of these, 4,856 patients had received dronedarone according to the Swedish Drug Register, and 170,139 patients who had not were used as a control population. Mean follow-up was 1.6 years, with a minimal follow-up of 6 months.
- Results** Patients prescribed dronedarone were younger (age 65.5 years vs. 75.7 years, $p < 0.0001$) and healthier than control patients. The annual mortality rate among patients who received dronedarone was 1.3% compared with 14.0% in the control population. There were no sudden cardiac deaths and no deaths related to liver failure among patients who received treatment with dronedarone. After propensity score matching and adjustment for cofactors, patients who received dronedarone had lower mortality than other AF patients (hazard ratio [HR]: 0.41; 95% confidence interval [CI]: 0.33 to 0.51). Dronedarone patients with heart failure had lower mortality than other heart failure patients (HR: 0.40; 95% CI: 0.30 to 0.53). They also had lower mortality than expected from the general population (standardized mortality ratio: 0.67; 95% CI: 0.55 to 0.78), which indicates the selection of low-risk patients. The risk of liver disease was not increased (HR: 0.57; 95% CI: 0.34 to 0.92).
- Conclusions** Dronedarone, as prescribed to AF patients in Sweden, has not exposed patients to increased risks of death or liver disease. (J Am Coll Cardiol 2014;63:2376–84) © 2014 by the American College of Cardiology Foundation

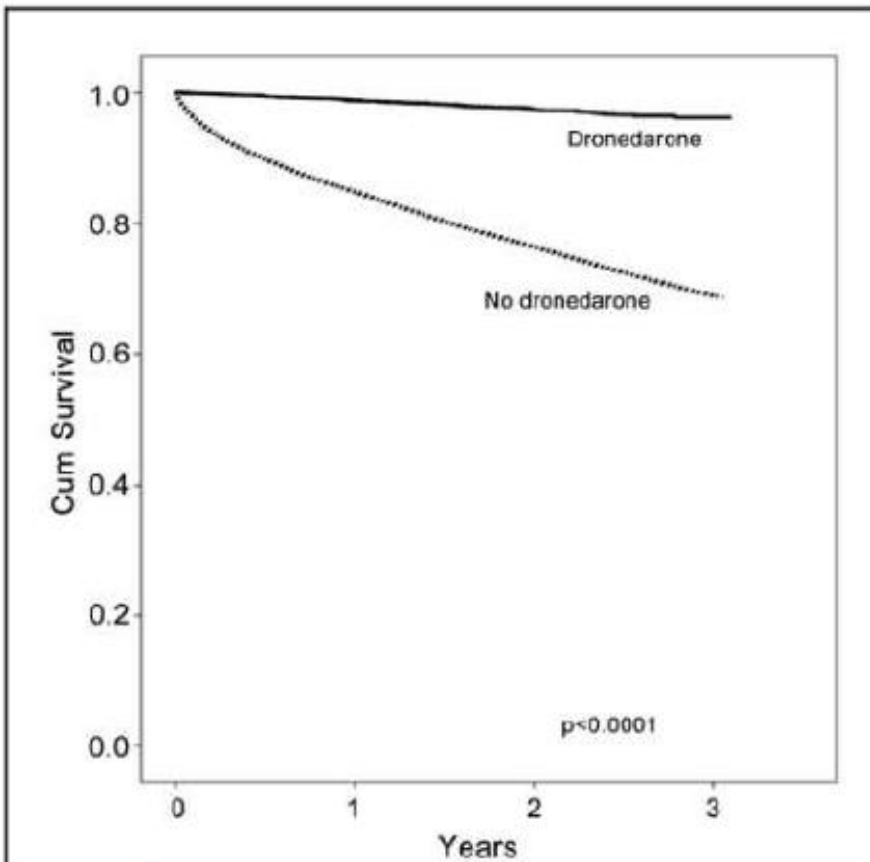


Figure 1 Unadjusted Mortality in Patients Exposed to Dronedarone

Unadjusted mortality in 4,856 patients with atrial fibrillation exposed to dronedarone compared with 170,139 patients with atrial fibrillation not exposed to dronedarone. Cum = cumulative.

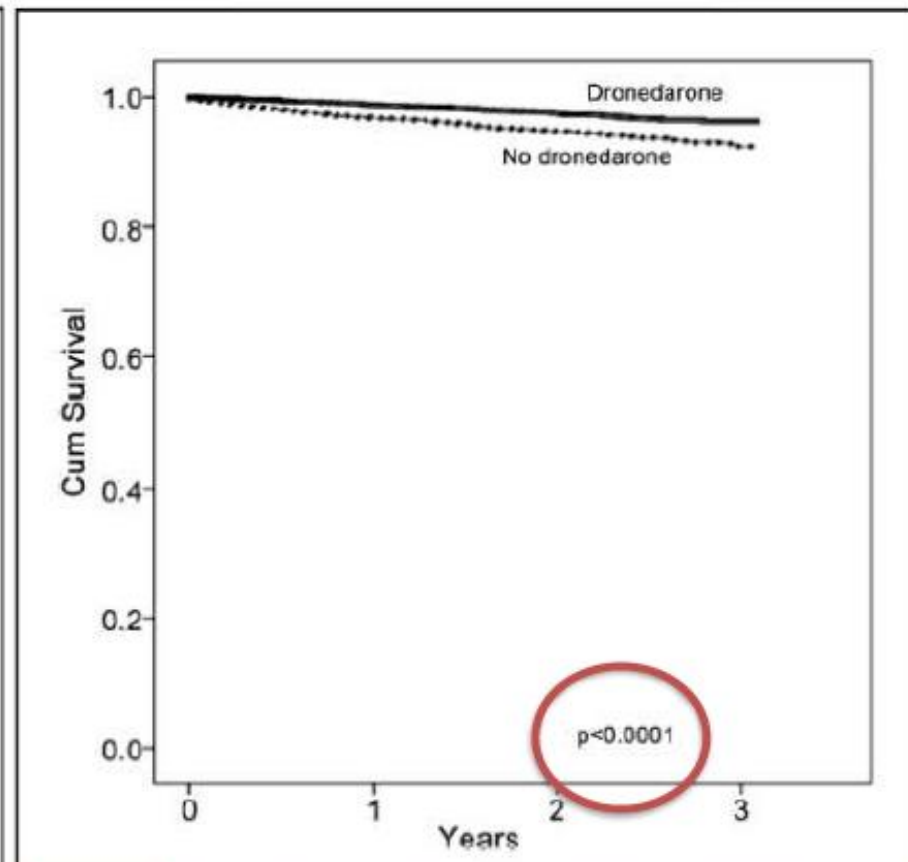


Figure 2 Unadjusted Mortality After Pairwise Matching for Propensity to Receive Dronedarone

Patients with atrial fibrillation exposed to dronedarone (n = 4,856) compared with patients with atrial fibrillation not exposed to dronedarone (n = 4,856). Cum = cumulative.

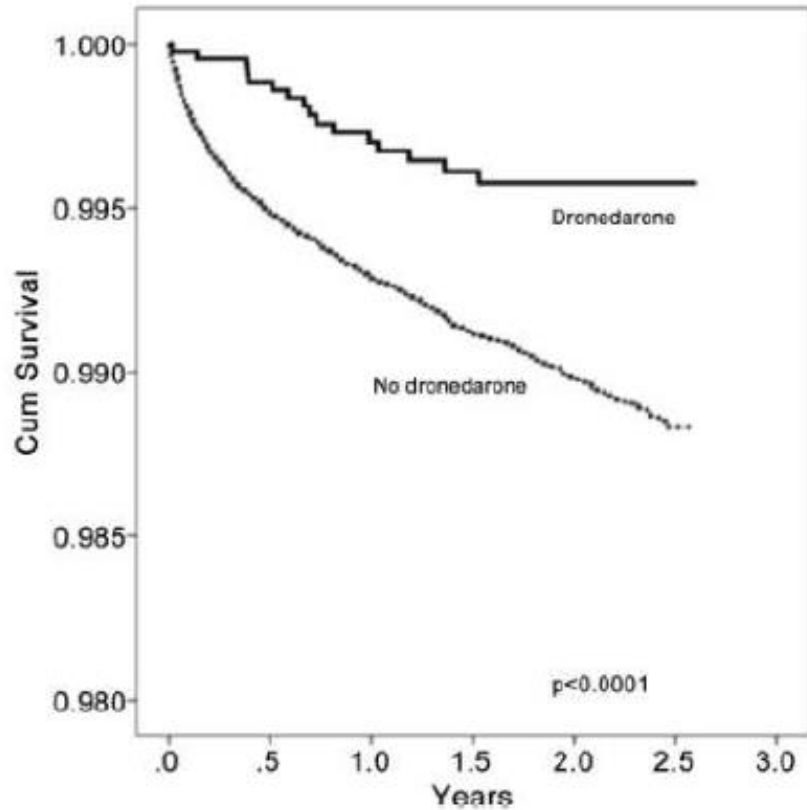


Figure 4

Unadjusted Incidence of Liver Disease in Patients Exposed to Dronedaron

Unadjusted incidence of liver disease in 4,856 patients with atrial fibrillation exposed to dronedaron compared with 170,139 patients with atrial fibrillation not exposed to dronedaron. Note abbreviation of scale. Cum = cumulative.

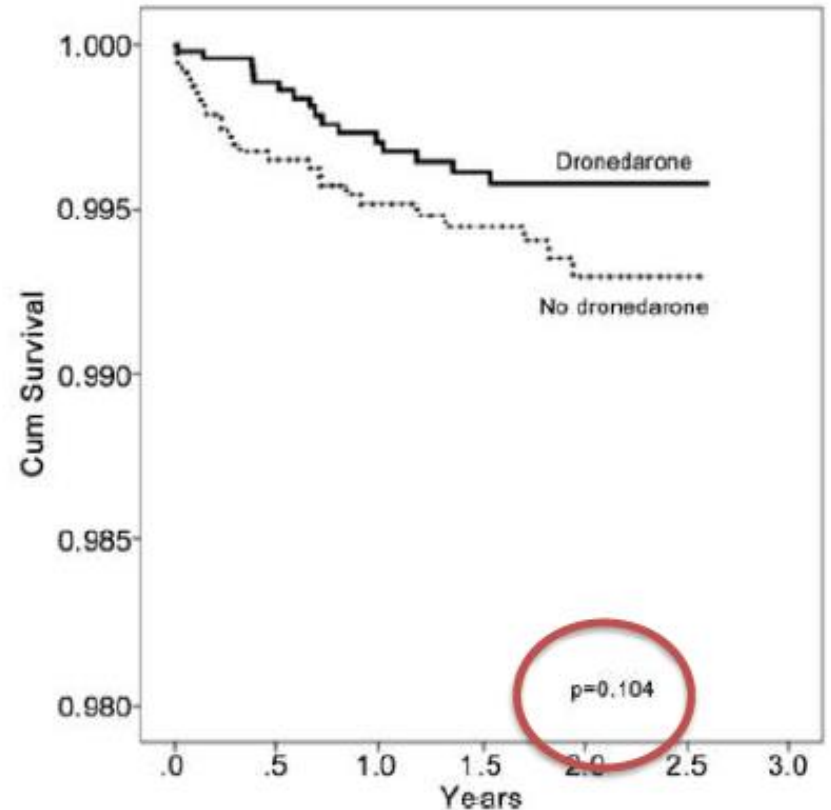
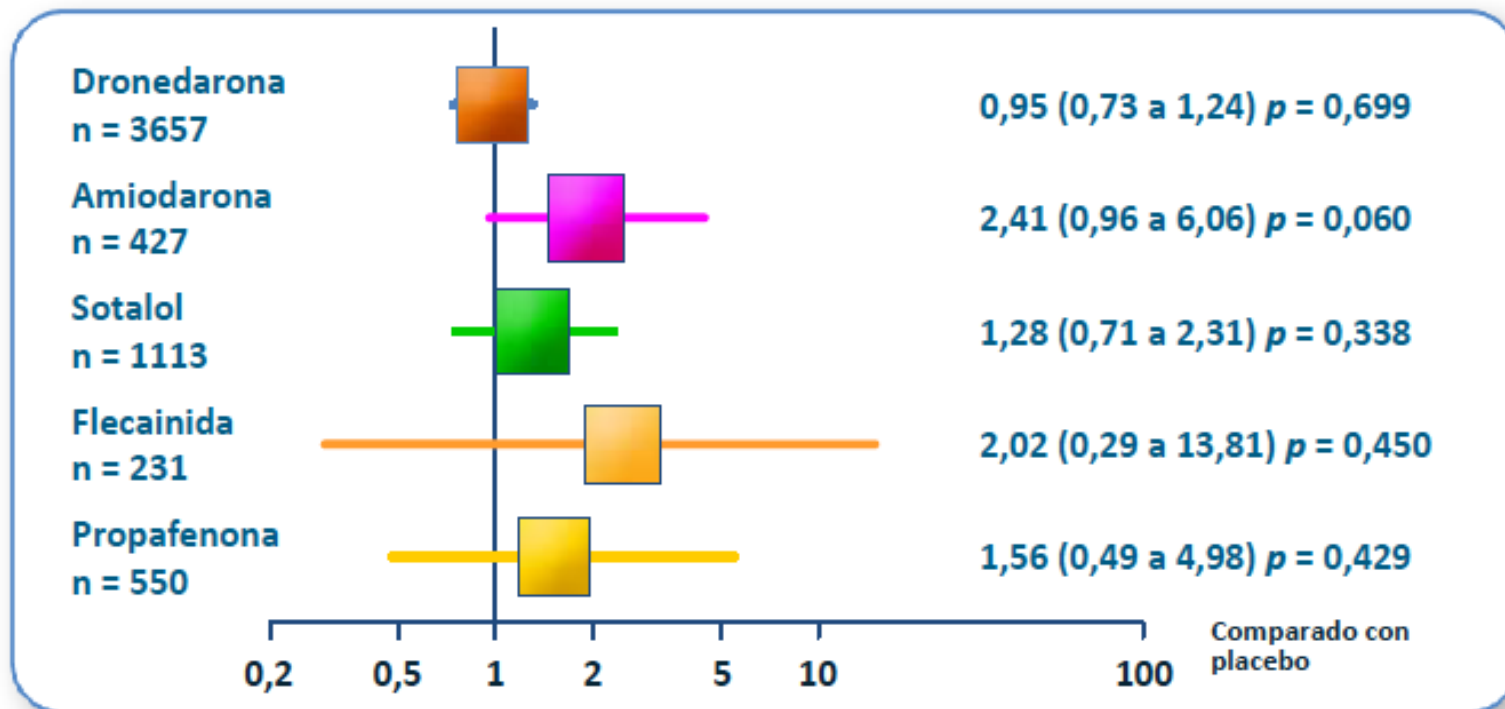


Figure 5

Unadjusted Incidence of Liver Disease After Pairwise Matching for Propensity to Receive Dronedaron

Comparison of 4,856 patients with atrial fibrillation exposed to dronedaron and 4,856 AF patients not exposed to dronedaron. Note abbreviation of scale. Cum = cumulative.

Dronedarona se asocia a menos eventos adversos graves comparado con otros FAA



Comparado con dronedarona Cociente de probabilidades (IC del 95%)	Acontecimientos adversos graves	Proarritmia
Amiodarona	2,53 (1,02–6,28)	3,75 (0,49–28,96)
Sotalol	1,35 (0,71–2,55)	4,43 (0,69–28,42)
Flecainida	2,12 (0,31–14,71)	4,65 (0,57–38,21)
Propafenona	1,64 (0,50–5,32)	2,79 (0,75–10,44)

Seguridad de Dronedarona en perspectiva

- **Muy bajo potencial proarritmogénico**
 - 1 caso en más de 7.200 pacientes en EE.CC.
- **Sin toxicidad extracardíaca conocida**
 - similar a placebo con seguimiento medio de 22 meses.
- **Diarreas**
 - leves y moderadas habitualmente, aparecen al inicio y autolimitadas con tratamiento habitual en 7-10 días.
- **Alteraciones hepatobiliares**
 - no identificadas en la fase preclínica y clínica, similares a placebo.
- **Plan de Minimización de Riesgos**
 - obligatorio EMA nuevos fármacos.
 - recoge la contraindicación (ICC), las interacciones y el aumento de creatinina

Datos Clínicos de Seguridad: EECC de dronedarona¹. Efectos Adversos Hepáticos

	Placebo (N=2.875)		Dronedarona 400 mg /12h (N=3.282)	
EA	73	(2.5%)	95	(2.9%)
EA grave	29	(1.0%)	28	(0.9%)
EA con discontinuación	7	(0.2%)	10	(0.3%)
EA grave con hospitalización	26	(0.9%)	28	(0.9%)
EA mortal	2	(<0.1)	1	(<0.1)

1 EECC: DAFNE, EURIDIS, ADONIS, ERATO, ATHENA

Conclusiones

- **Ensayos clínicos:**
 - Dronedarona el FAA mejor y mas estudiado en la FA
 - Indicaciones clínicas precisas (No ICC, No FA PM)
- **Gran experiencia clínica actual (USA, Alemania, España)**
- **Registros del mundo real han valido los resultados de los ensayos clínicos en:**
 - Eficacia (hospitalizaciones, mortalidad CV)
 - Seguridad