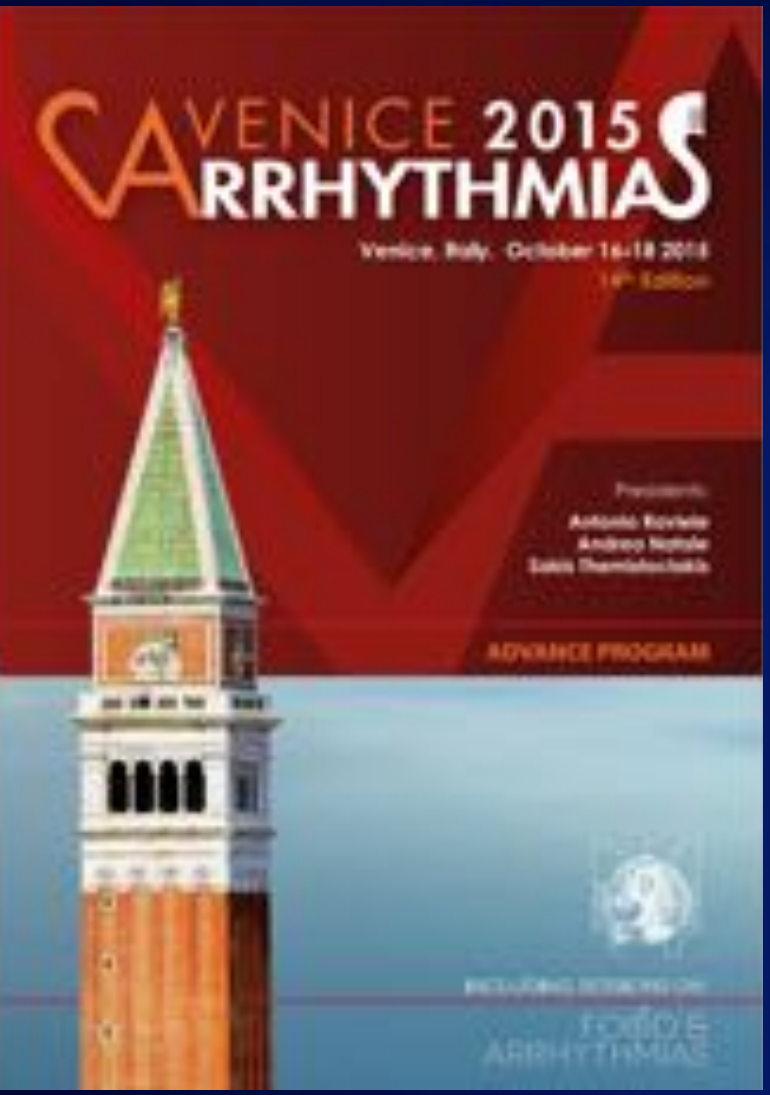

Increased mortality with dronedarone: is digoxin the cause?

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October 16 - 18
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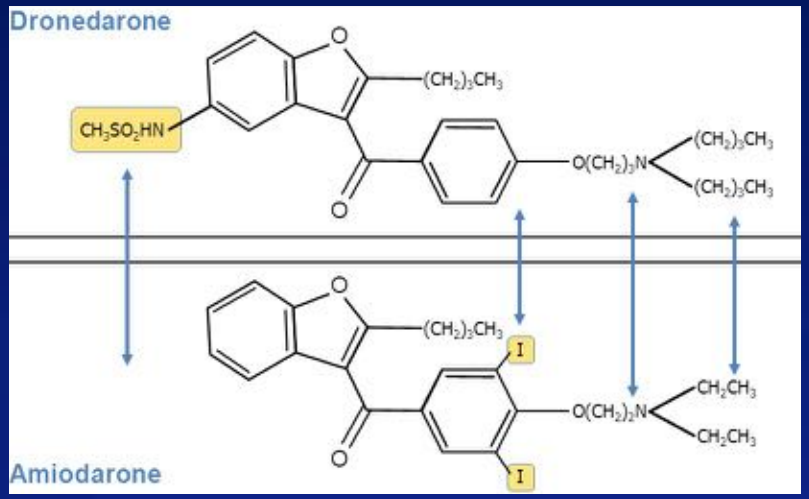
NO CONFLICT OF INTEREST TO DECLARE

DRONEDARONE

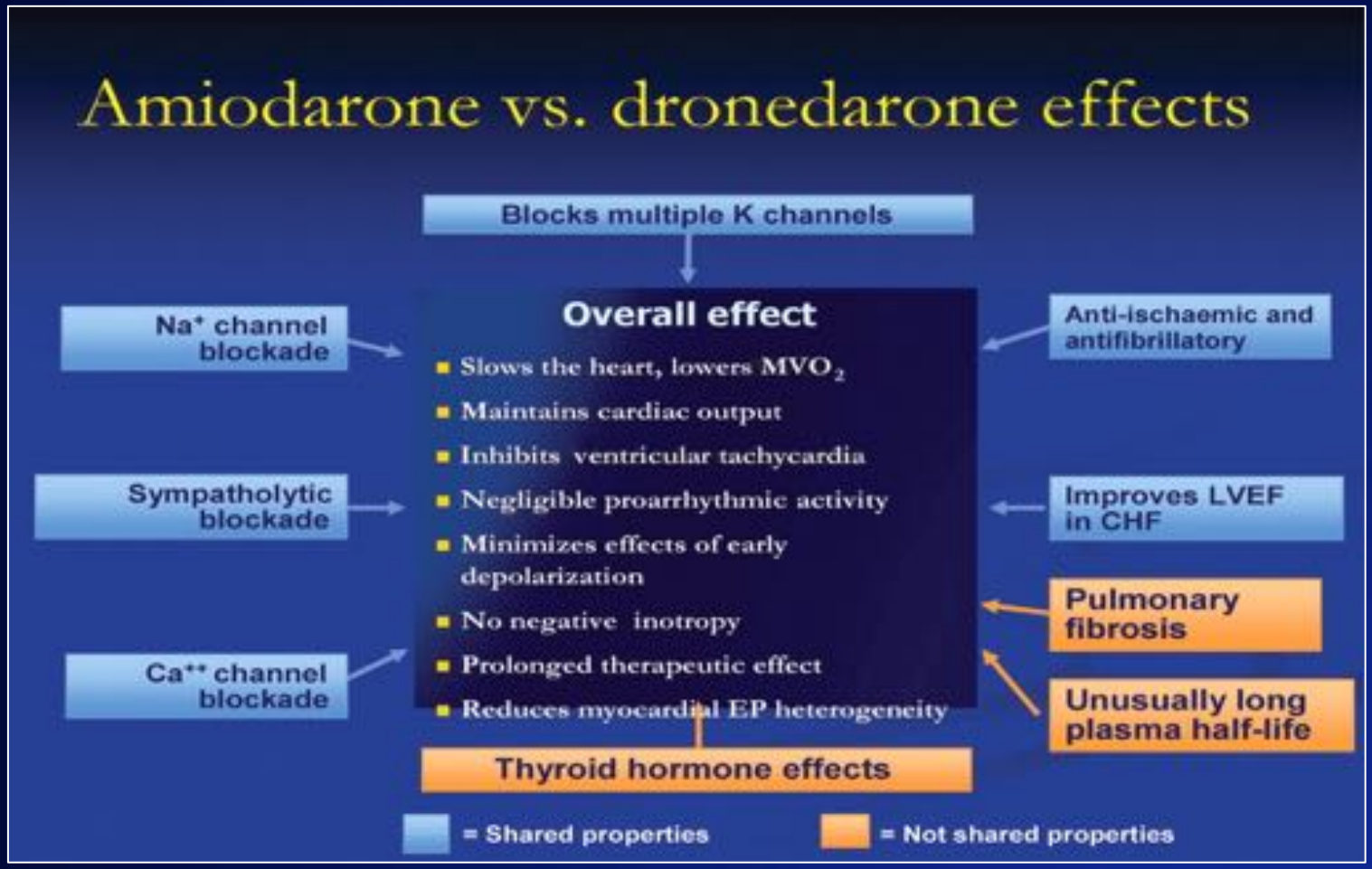
Dronedarone is a noniodinated benzofuran derivative related to amiodarone

- class I-IV antiarrythmic activity
- antiadrenergic effects
- antifibrillatory effects on the atrial and ventricular myocardium
- no iodine-related organ toxicity, a decreased lipophilicity and a shortened half-life



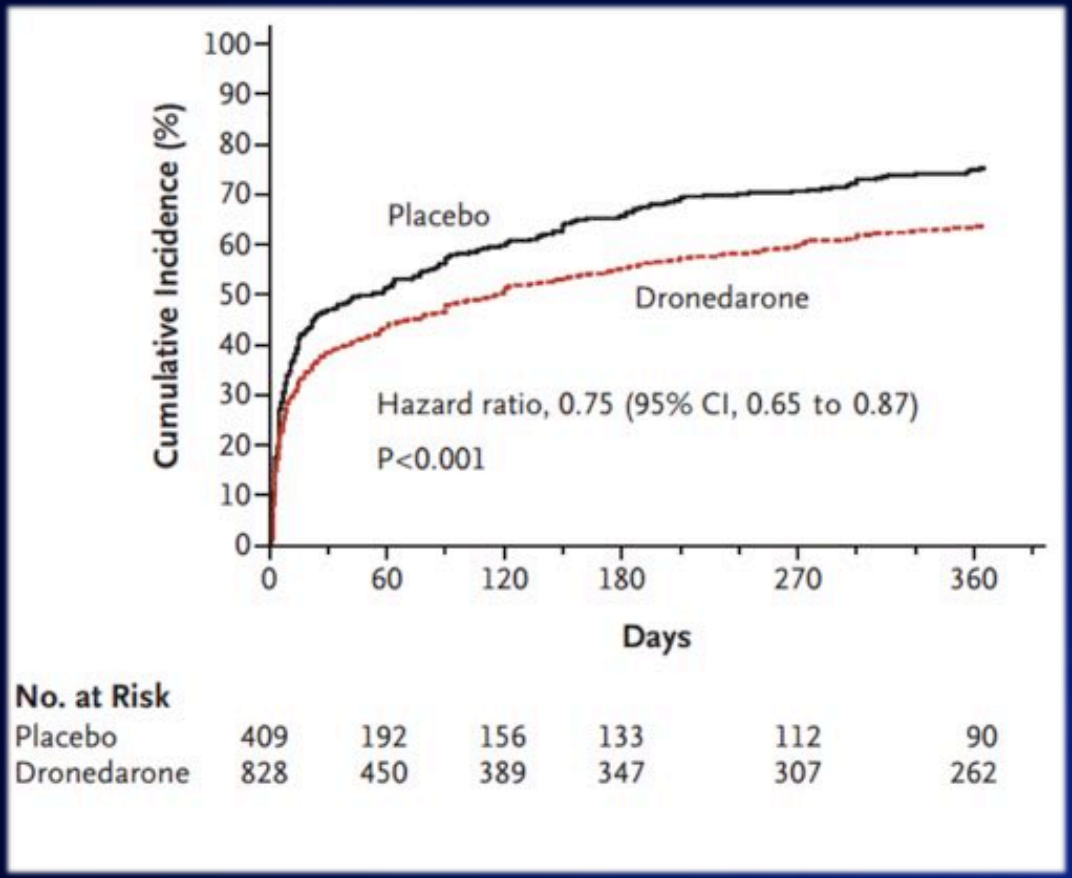
Kathofer et al. Cardiovasc Drug Rev.2005;23(3):217-30

Comparison of some major pharmacodynamic properties of dronedarone and amiodarone



Bramah N. Singh, and Etienne Aliot Eur Heart J Suppl 2007;9:G17-G25

EURIDIS/ADONIS



Dronedarone Showed a Significant Reduction in First AF Recurrence in Combined Analysis

Singh BN, et al. N Engl J Med. 2007;357:987-99

Efficacy and Safety of Dronedarone in Patients Previously Treated With Other Antiarrhythmic Agents

Federico Guerra, MD; Stefan H. Hohnloser, MD; Peter R. Kowey, MD; Harry J. G. M. Crijns, MD; Etienne M. Aliot, MD; David Radzik, MD; Denis Roy, MD; Stuart Connolly, MD; Alessandro Capucci, MD

POST HOC analysis of data from the EURIDIS and ADONIS trials

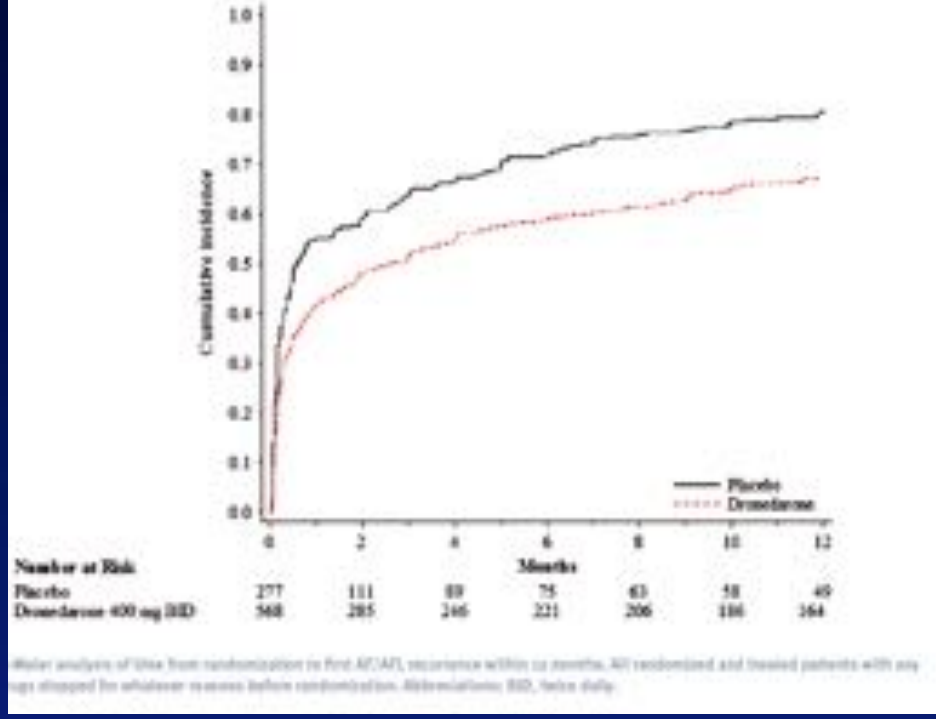
The aim of this post hoc analysis was to evaluate the efficacy and safety of dronedarone in patients previously treated with AADs, with a specific focus on class Ic AADs or sotalol

The primary end point was AF/AFL recurrence in patients previously treated with another AAD that was discontinued for whatever reason prior to randomization.

Guerra F, Capucci A et al Clin. Cardiol. 37, 12, 717–724; 2014

Results

In patients previously treated with ***any AADs****, dronedarone decreased the risk of AF recurrence by 30.4% vs placebo (HR 0.70; P < 0.001)*



In patients previously treated with a ***class Ic*** agent, dronedarone decreased the risk of recurrence by 31.4% (HR: 0.69; *P* = 0.004)

In patients previously treated with ***sotalol***, dronedarone showed a trend toward a decrease of risk of recurrence (HR: 0.86; *P* = 0.244)

Guerra F, Capucci A et al Clin. Cardiol. 37, 12, 717–724

Results (secondary end points)

In patients previously treated with another antiarrhythmic agent that was **discontinued for lack of efficacy** at any time prior to randomization, **dronedarone decreased the risk of AF/AFL recurrence by 22.9%** in comparison to placebo (*P* =0.023)

In patients previously treated with another antiarrhythmic agent that was **discontinued for an AE** at any time prior to randomization, **dronedarone decreased the risk of AF/AFLrecurrence by 38.9%** in comparison to placebo (*P* =0.006)

Guerra F, Capucci A et al Clin. Cardiol. 37, 12, 717–724

The relative risk of AEs in patients treated with dronedarone was similar to the relative risk of patients randomized to placebo, irrespective of previous treatment with class Ic or sotalol, as shown by the confidence intervals

Table 2. Overview of Adverse Events, Excluding AF/AFL Events, According to Class Ic or Sotalol Before Randomization

	Class Ic or Sotalol Before Randomization			No Class Ic or Sotalol Before Randomization		
	Placebo, n = 179	Dronedarone, 400 mg BID, n = 332	RR [95% CI][a]	Placebo, n = 230	Dronedarone, 400 mg BID, n = 496	RR [95% CI][a]
TEAE[b]	102 (57.0%)	200 (60.2%)	1.06 [0.91-1.23]	155 (67.4%)	358 (72.2%)	1.07 [0.96-1.19]
Serious TEAE	23 (12.8%)	31 (9.3%)	0.73 [0.44-1.21]	41 (17.8%)	87 (17.5%)	0.98 [0.70-1.38]
AE leading to premature study drug discontinuation[b]	8 (4.5%)	27 (8.1%)	1.82 [0.84-3.92]	17 (7.4%)	53 (10.7%)	1.45 [0.86-2.44]
Serious TEAE leading to hospitalization	22 (12.3%)	29 (8.7%)	0.71 [0.42-1.20]	38 (16.5%)	79 (15.9%)	0.96 [0.68-1.37]
Serious TEAE leading to death	0	2 (0.6%)	NA	4 (1.7%)	7 (1.4%)	0.81 [0.24-2.74]

Abbreviations: AE, adverse event; AF, atrial fibrillation; AFL, atrial flutter; BID, twice daily; CI, confidence interval; NA, not applicable; RR, relative risk; SAEs, serious adverse events; TEAE, treatment-emergent adverse event.

[a]RR estimates with 95% CI: dronedarone 400 mg BID vs placebo. [b] Including SAEs.

Guerra F, Capucci A et al Clin. Cardiol. 37, 12, 717–724

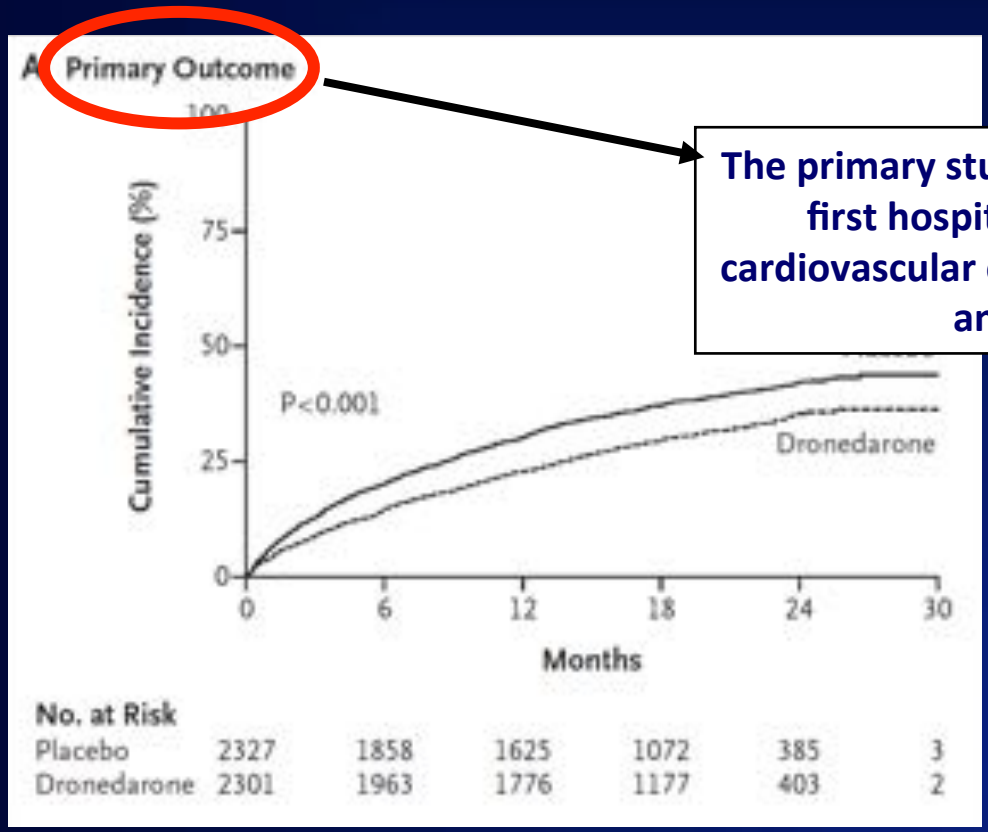
- In this post hoc analysis, dronedarone was shown to be effective in maintaining sinus rhythm in patients who suspended other AADs, irrespective of reason (including tolerability issues or lack of efficacy).

- As AF patients frequently switch antiarrhythmic agents for rhythm control, the present benefit/risk data provide further evidence to suggest that *dronedarone is an important therapeutic option also in non-naive patients*

- This crucial last point underlines the role of *dronedarone as a possible therapeutic option even in eligible patients who had already experienced a recurrence with another antiarrhythmic drug*, whether amiodarone, sotalol, or class Ic agents.

Guerra F, Capucci A et al Clin. Cardiol. 37, 12, 717–724

ATHENA (A placebo-controlled, double-blind,parallel arm Trial to assess the efficacy of Dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/Atrial flutter)

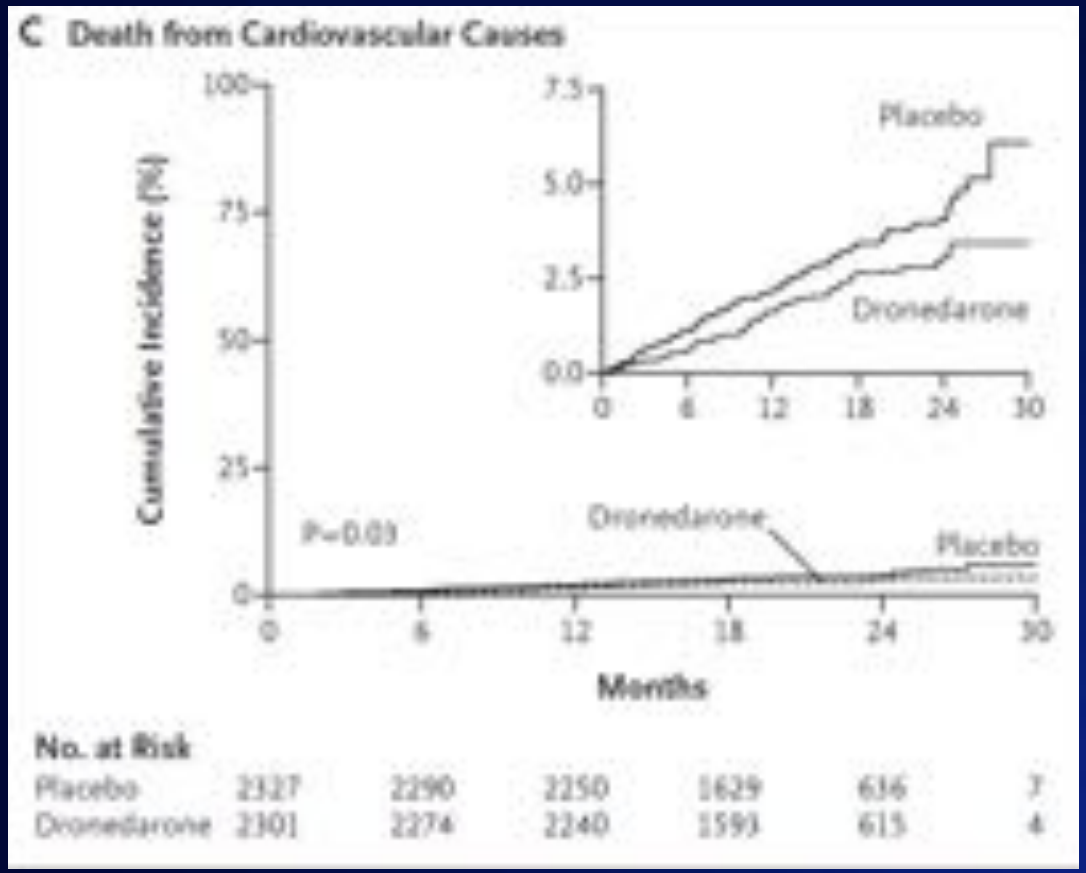


The primary study outcome was the first hospitalization due to cardiovascular events or death from any cause

Dronedarone Significantly Decreased Risk of CV Hospitalisation or Death by 24%
(HR 0.76, p<0.001)

Hohnloser SH et al. N Engl J Med 2009;360:668-78.

ATHENA

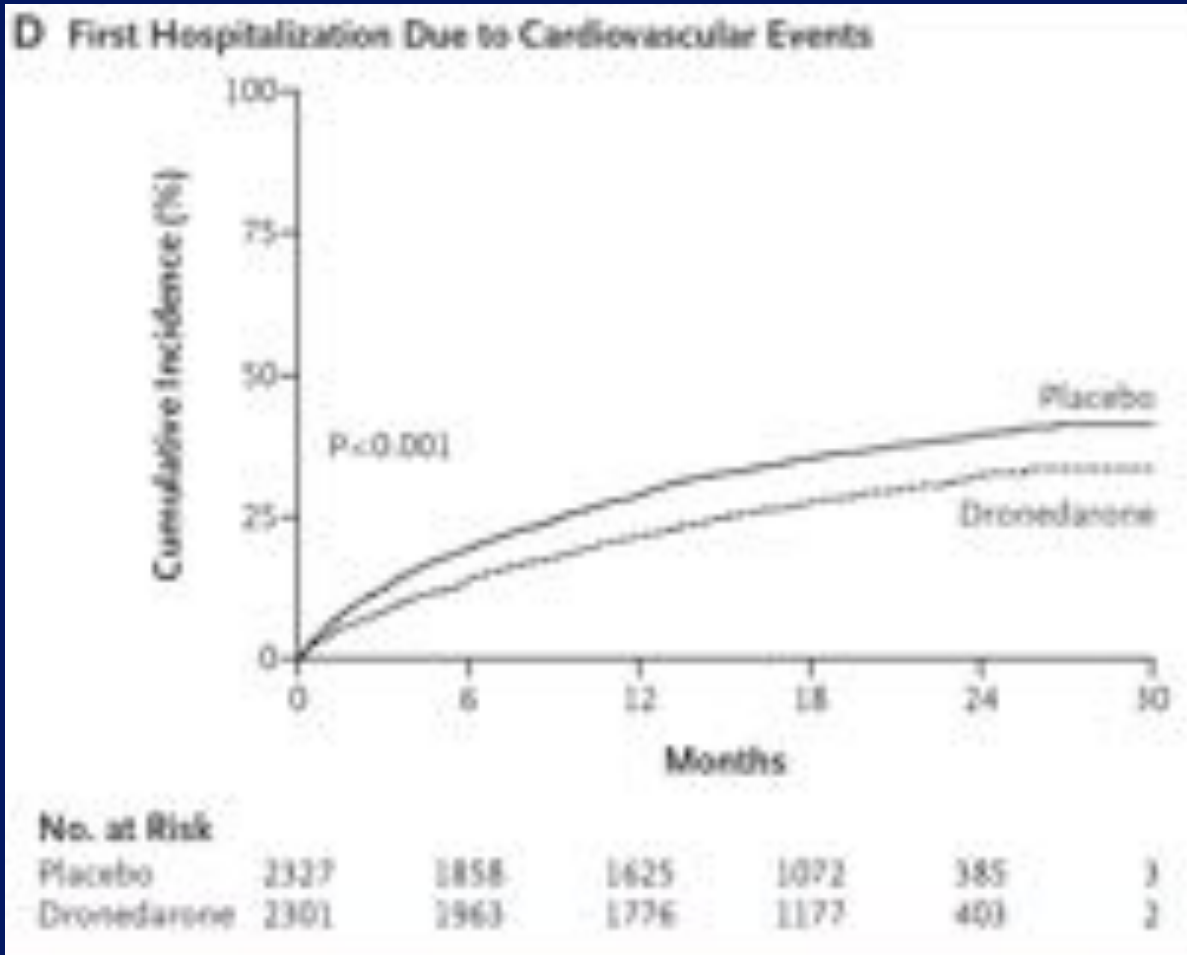


Dronedarone Significantly Decreased Risk of Death from CV causes by 29% (HR 0.71, p=0.03)

Hohnloser SH et al. N Engl J Med 2009;360:668-78.

ATHENA

Dronedarone Significantly Decreased Risk of First CV Hospitalization by 26%
(HR 0.74, p<0.001)



Hohnloser SH et al. N Engl J Med 2009;360:668-78

ATHENA

Dronedarone Significantly Decreased Risk of Stroke by 34%

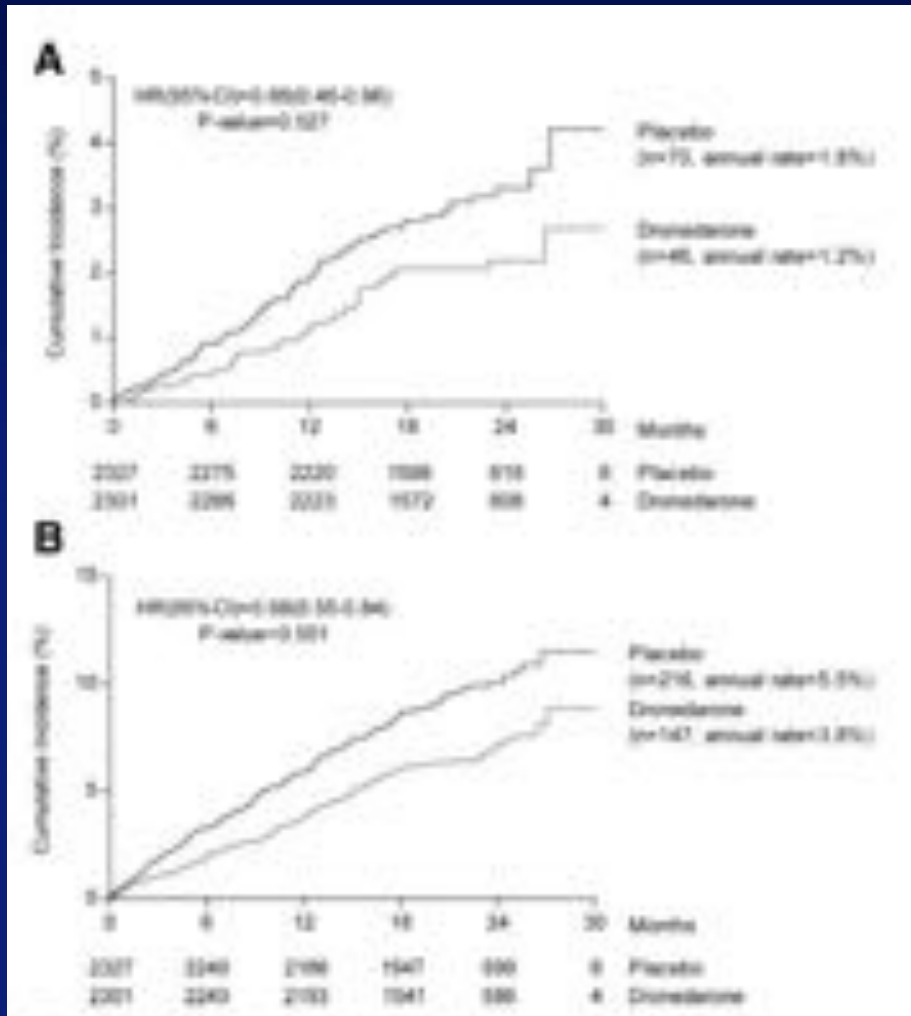
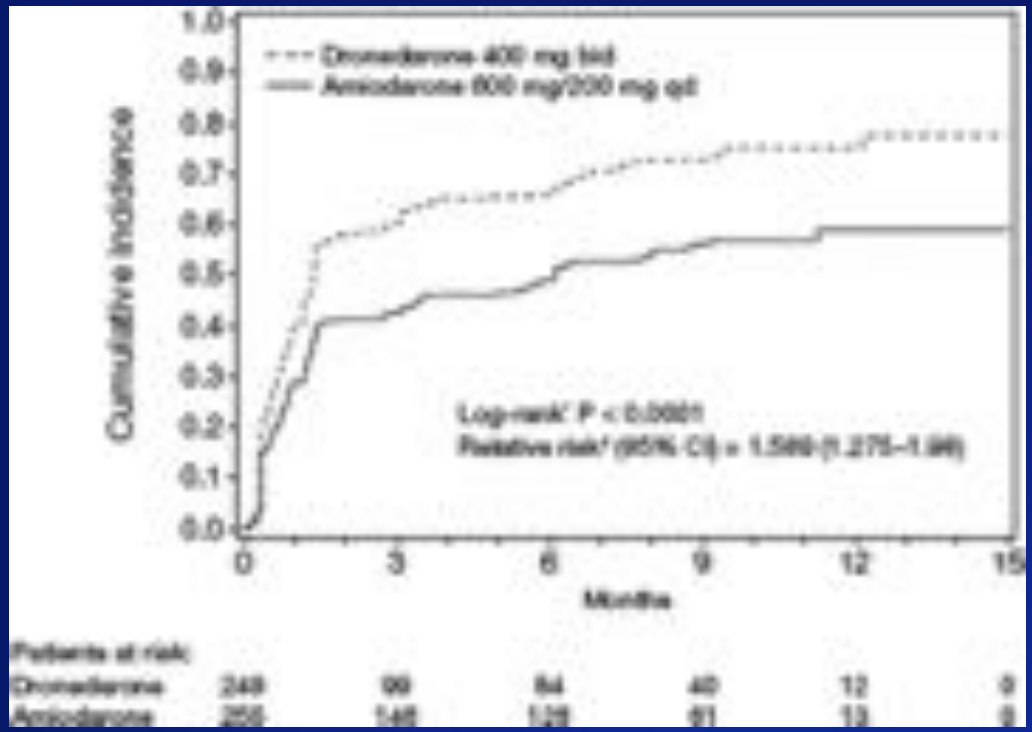


Figure 2. Cumulative risk of stroke (A) and composite outcome of stroke, acute coronary syndrome, or cardiovascular death (B). HR indicates hazard ratio.

Stuart J. Connolly et al.Circulation 2009; 120:1174-1180

and Safety of Dronedarone **versus Amiodarone** in Patients with Persistent Atrial Fibrillation: The **DIONYSOS** Study

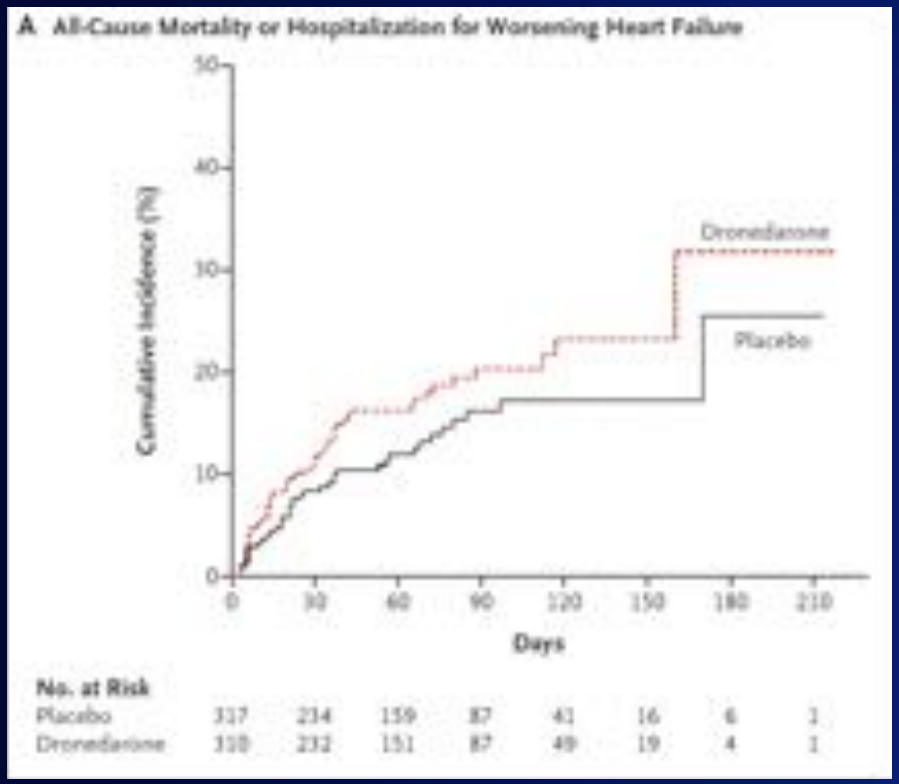
Primary Endpoint: More AF Events But Less Early Discontinuation With Dronedarone



Le Heuzey J.Y. et al., J. Cardiovasc. Electrophysiol. 2010; 21 :597-605

ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse)

Double blind, randomized placebo controlled trial in patients *recently hospitalized with congestive cardiac failure and severe impairment of left ventricular systolic function (EF 35%)*



The primary outcome was a composite of all cause mortality and hospitalization for heart failure

The study was terminated prematurely 7 months after commencing due to excess mortality in the Dronedarone group

Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008 Jun 19;358(25):2678-87.

ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating Morbidity DecreAse)

Table 2. Cause of Death.

Cause	Dronedarone Group (N = 310)	Placebo Group (N = 317)
	no. (%)	
Cardiovascular	24 (7.7)	9 (2.8)
Myocardial infarction	0	2 (0.6)
Progressive heart failure	10 (3.2)	2 (0.6)
Documented arrhythmia	6 (1.9)	2 (0.6)
Other cardiovascular cause	3 (1.0)	0
Presumed cardiovascular cause	5 (1.6)	3 (0.9)
Arrhythmia or sudden death*	10 (3.2)	6 (1.9)
Noncardiovascular	1 (0.3)	3 (0.9)
Total	25 (8.1)	12 (3.8)

There was no significant difference between the two groups in the rates of arrhythmic or sudden death

Worsening heart failure contributed to the majority of the excess events

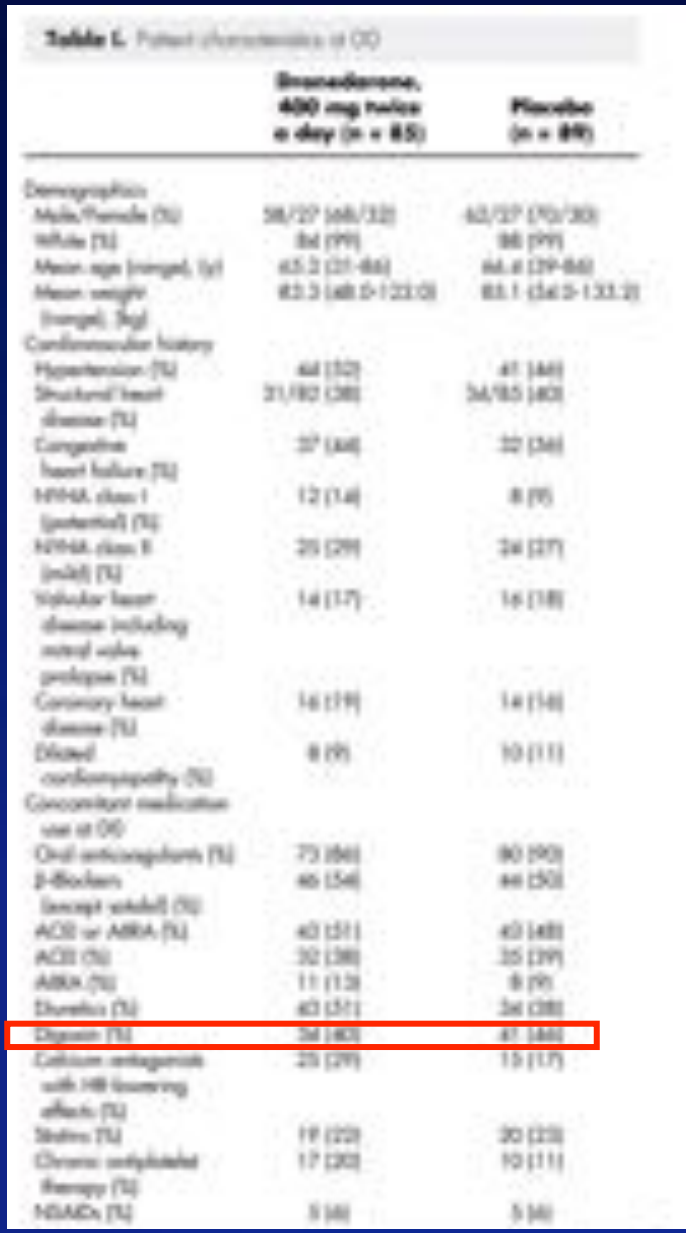
Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008 Jun 19;358(25):2678-87.

Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (**ERATO**) study

Methods In this randomized, double-blind, multinational trial, dronedarone, 400 mg twice a day (n = 85), or matching placebo (n = 89) was administered for 6 months to adult patients with permanent AF, in addition to standard therapy

Conclusion In addition to its reported rhythm-targeting and rate-targeting therapeutic actions in paroxysmal and persistent AF, dronedarone improves ventricular rate control in patients with **permanent AF**

Dronedarone was well tolerated with no evidence of organ toxicities or proarrhythmias in this short-term study



Davy JM, Herold M, Hoglund C, et al. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J 2008;156(3):527 e1-9.

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)

Based on the excellent results of the ATHENA trial (even in the subgroup of patients that developed permanent AF during the study)

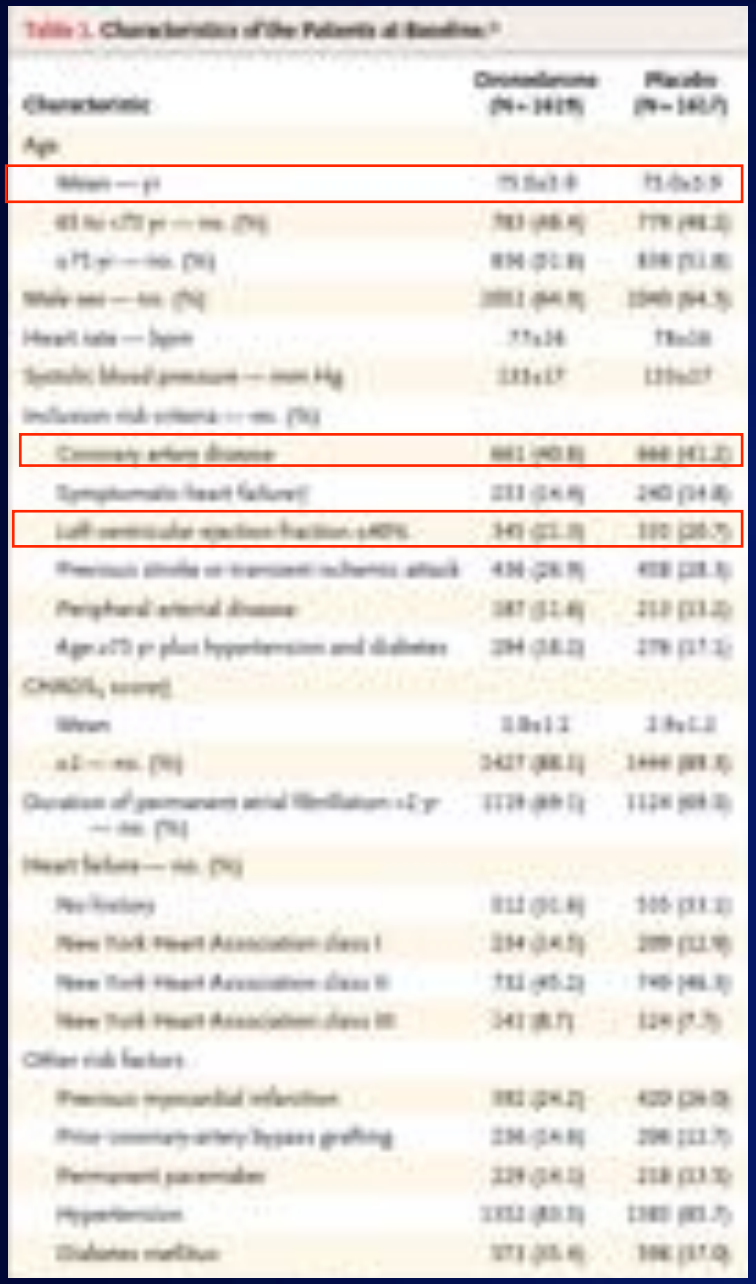
PALLAS was designed to determine if dronedarone would reduce major vascular events or unplanned hospitalization for cardiovascular causes in patients with permanent AF

Two co-primary outcomes

- a composite of stroke, myocardial infarction, systemic embolism or cardiovascular death
- unplanned hospitalization for cardiovascular causes or death

Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in highrisk permanent atrial fibrillation. N Engl J Med 2011; 365(24):2268-76.

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)



Characteristic	Dronedarone	Placebo
Age		
Mean — yr		
65 to <75 yr — no. (%)		
≥75 yr — no. (%)		
Male sex — no. (%)		
Heart rate — bpm		
Systolic blood pressure — mm Hg		
Inclusion risk criteria — no. (%)		
Coronary artery disease		
Symptomatic heart failure		
Left ventricular ejection fraction ≤40%		
Previous stroke or transient ischemic attack		
Peripheral arterial disease		
Age ≥75 yr plus hypertension and diabetes		
$CHADS_2$ score		
Mean		
≥2 — no. (%)		
Duration of permanent atrial fibrillation >2 yr — no. (%)		
Heart failure — no. (%)		
No history		
New York Heart Association class I		
New York Heart Association class II		
New York Heart Association class III		
Other risk factors		
Previous myocardial infarction		
Prior coronary-artery bypass grafting		
Permanent pacemaker		
Hypertension		
Diabetes mellitus		

Compared to ATHENA patients, PALLAS patients were older, had more coronary artery disease, stroke and had more evidence of left ventricular dysfunction

Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in highrisk permanent atrial fibrillation. N Engl J Med 2011; 365(24):2268-76.

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)

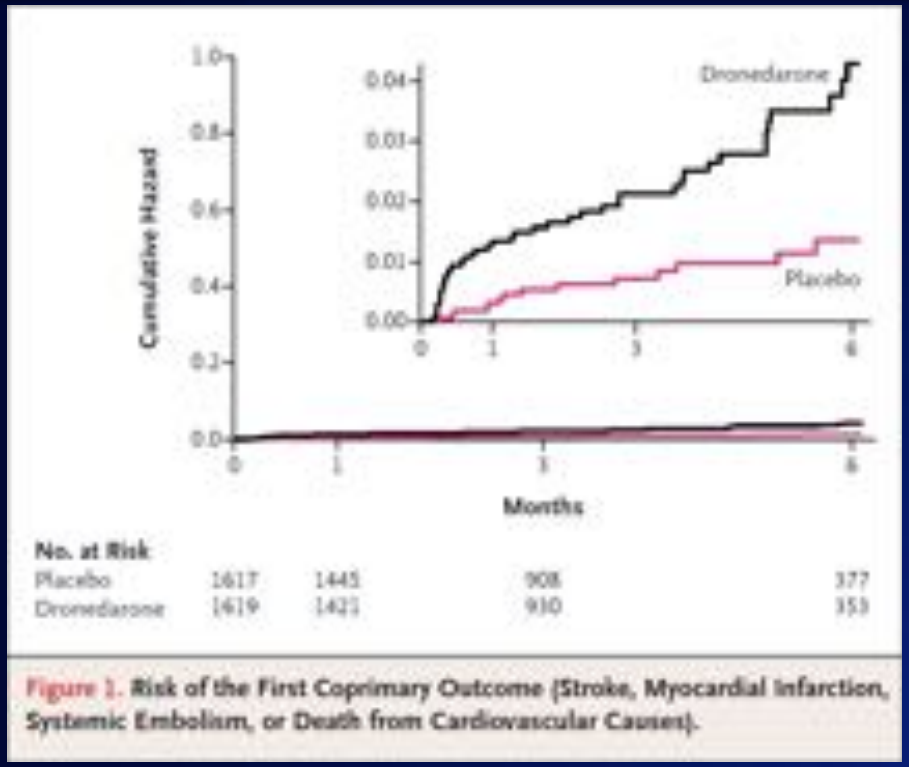


Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

PALLAS was terminated prematurely after the enrollment of 3236 patients, well short of the planned 10,800 patients, because of safety concerns and an increase in the first co-primary outcome (HR 2.29, p= 0.002)

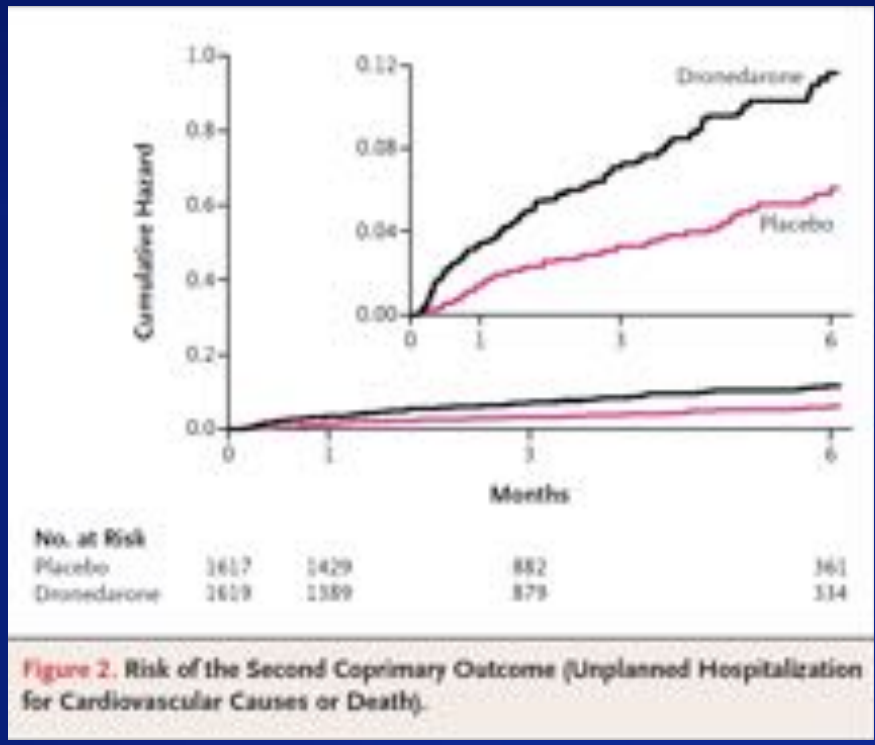


Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

There were also statistically significant increases in death of any cause, death from cardiovascular causes, death from cardiac arrhythmia, stroke, unplanned hospitalization for cardiovascular causes, hospitalization for heart failure and heart failure episodes of hospitalization (HR 1.95, p<0.001)

Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in highrisk permanent atrial fibrillation. N Engl J Med 2011; 365(24):2268-76.

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)

The increased mortality in the ANDROMEDA trial was predominantly due to worsening heart failure without an increase in arrhythmic death

In contrast excess mortality in the PALLAS trial was attributed primarily to arrhythmic death

This may not be solely due to the use of Dronedarone in the presence of LV dysfunction and CHF

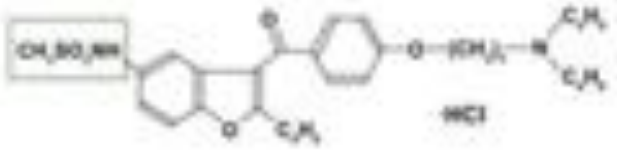
Table 2. Study Outcomes.*

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI)†	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–3.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046
From arrhythmia	13	2.5	4	0.8	3.26 (1.06–10.0)	0.03
Stroke						
Any‡	23	4.4	10	1.9	2.32 (1.11–4.88)	0.02
Ischemic	18	3.4	9	1.7	2.01 (0.90–4.48)	0.08
Systemic embolism	1	0.2	0	0.0	NA	NA
Myocardial infarction or unstable angina	15	2.9	8	1.5	1.89 (0.80–4.45)	0.14
Myocardial infarction	3	0.6	2	0.4	1.54 (0.26–9.21)	0.63
Unplanned hospitalization for cardiovascular causes	113	22.5	59	11.4	1.97 (1.44–2.70)	<0.001
Hospitalization for heart failure	43	8.3	24	4.6	1.81 (1.10–2.99)	0.02
Heart-failure episode or hospitalization§	115	23.2	55	10.7	2.16 (1.57–2.98)	<0.001

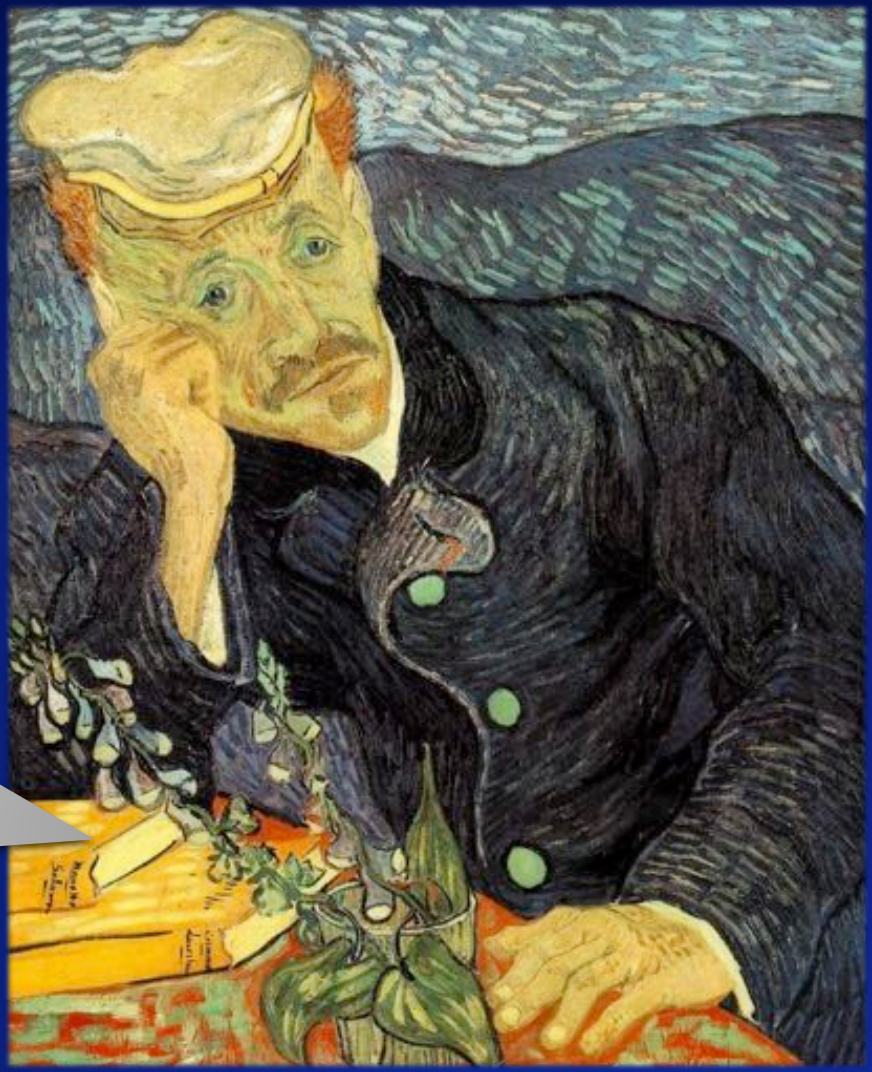
Pradyot Saklani and Allan Skanes. Current Cardiology Reviews, 2012, 8, 302-309

Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in highrisk permanent atrial fibrillation. N Engl J Med 2011; 365(24):2268-76.

Dronedarone



HOW DO DRONEDARONE AND DIGOXIN INTERACT WITH EACH OTHER?



One hypothesis is the proposed metabolic interaction between Dronedarone and Digoxin

Dronedarone increases the serum digoxin level through a P-glycoprotein interaction, and digoxin toxicity is associated with life-threatening ventricular arrhythmia and conduction block.

….and we know that digoxin has a **narrow therapeutic index**…

Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in highrisk permanent atrial fibrillation. N Engl J Med 2011; 365(24):2268-76.


Table 1 Patient demographics and baseline medication in the different trials

DAFNE | EURIDIS | ADONIS | ERATO | ANDROMEDA | ATHENA | PALLAS

In PALLAS, almost one third of patients were receiving digoxin and in these patients dronedarone increased digoxin serum levels by 33% (1.2 ng/ml vs 0.9 ng/ml; p<0.001) *

Stefan H. Hohnloser et al. Europace (2014) 16, 1117–1124

** Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in highrisk permanent atrial fibrillation. N Engl J Med 2011; 365(24):2268-76.*

Interaction Between Digoxin and Dronedarone in the PALLAS Trial

Stefan H. Hohnloser, MD; Jonathan L. Halperin, MD; A. John Camm, MD; Peggy Gao, MSc; David Radzik, MD; Stuart J. Connolly, MD; on behalf of the PALLAS investigators*

SUBGROUP ANALYSIS

Table 1 Baseline Data

Variable	Dronedarone (n=1619) Baseline Digoxin Use: Yes	Dronedarone (n=1619) Baseline Digoxin Use: No	P Value	Placebo (n=1617) Baseline Digoxin Use: Yes	Placebo (n=1617) Baseline Digoxin Use: No	P Value
Age, y (mean, SD)	74.6 (5.8)	75.1 (5.9)	0.12	75.1 (5.9)	74.9 (6.0)	0.48
Heart rate, beats per minute (mean, SD)	79.0 (16.8)	76.8 (14.7)	0.004	78.3 (15.3)	77.7 (15.0)	0.46
Blood pressure, systolic, mm Hg (mean, SD)	133.2 (16.9)	133.1 (16.9)	0.96	132.1 (16.2)	133.0 (17.3)	0.31
Duration of permanent AF >2 y	392 (72.1%)	727 (67.8%)	0.08	374 (71.2%)	750 (68.9%)	0.33
Male sex	323 (59.4%)	728 (67.7%)	0.001	296 (56.3%)	744 (68.2%)	<0.0001
Heart Failure			Overall P<0.0001			<0.0001
No history	139 (25.6%)	373 (34.7%)	<0.0001	142 (27.0%)	393 (36.0%)	<0.0001
NYHA Class I	78 (14.3%)	156 (14.5%)	0.93	62 (11.8%)	147 (13.5%)	0.34
NYHA Class II	258 (47.4%)	474 (44.1%)	0.20	261 (49.6%)	488 (44.7%)	0.07
NYHA Class III	69 (12.7%)	72 (6.7%)	<0.0001	61 (11.6%)	63 (5.8%)	<0.0001
LVEF ≤40%	151 (27.8%)	194 (18.0%)	<0.0001	133 (25.3%)	202 (18.5%)	0.002
CAD	182 (33.5%)	479 (44.6%)	<0.0001	181 (34.4%)	485 (44.5%)	<0.0001
Prior myocardial infarction	117 (21.5%)	275 (25.6%)	0.07	138 (26.2%)	282 (25.8%)	0.87
Permanent pacemaker	69 (12.7%)	160 (14.9%)	0.23	61 (11.6%)	157 (14.4%)	0.12
Hypertension	447 (82.2%)	905 (84.2%)	0.30	440 (83.7%)	845 (86.6%)	0.111
Receiving a β-blocker	403 (74.1%)	798 (74.2%)	0.95	375 (71.3%)	826 (75.7%)	0.06
Receiving either verapamil or diltiazem	57 (10.5%)	113 (10.5%)	0.99	59 (11.2%)	103 (9.4%)	0.27
Receiving a diuretic	387 (73.2%)	706 (65.7%)	0.003	386 (73.4%)	707 (64.8%)	0.001
Receiving an ACE inhibitor	296 (54.4%)	530 (49.3%)	0.05	260 (49.4%)	569 (52.2%)	0.31
Receiving an angiotensin receptor blocker	131 (24.1%)	290 (27.0%)	0.21	125 (23.8%)	286 (26.2%)	0.29

There were no significant differences in patient characteristics for dronedarone vs placebo in the digoxin and in the no-digoxin subgroups. The rate of prior myocardial infarction is not significantly different in the dronedarone and placebo group within the digoxin subgroup (21.5% vs 26.2%; P=0.07).
ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; CAD, coronary artery disease; NYHA, New York Heart Association; and LVEF, left ventricular ejection fraction.

Table 3. Fatal Events According to Baseline Digoxin Use

Outcome	Placebo Events/N	Placebo Number of Events per 100 Patient-Months*	Dronedarone Events/N	Dronedarone Number of Events per 100 Patient-Months*	Dronedarone vs Placebo HR	95% CI	P Value
All-cause mortality (interaction P=0.02)							
Overall	13/1617	0.2	25/1619	0.39	1.94	0.99–3.79	0.05
No digoxin	10/1091	0.23	8/1075	0.19	0.82	0.32–2.08	0.67
Digoxin at baseline	3/526	0.15	17/544	0.81	5.47	1.60–18.66	0.007
Cardiovascular death (interaction P=0.02)							
Overall	10/1617	0.16	21/1619	0.33	2.11	1.00–4.49	0.05
No digoxin	8/1091	0.16	6/1075	0.14	0.76	0.26–2.19	0.61
Digoxin at baseline	2/526	0.10	15/544	0.72	7.24	1.65–31.67	0.009
Arrhythmic death (interaction P=0.002)							
Overall	4/1617	0.06	13/1619	0.21	3.26	1.06–10.00	0.04
No digoxin	4/1091	0.09	2/1075	0.05	0.51	0.09–2.76	0.43
Digoxin at baseline	0/526	0.0	11/544	0.53	22.701	1.35–386.171	0.03
Non-cardiovascular mortality (interaction P=0.682)							
Overall	3/1617	0.05	4/1619	0.06	1.35	0.30–6.04	0.69
No digoxin	2/1091	0.06	2/1075	0.05	1.06	0.15–7.51	0.96
Digoxin at baseline	1/526	0.05	2/544	0.18	1.93	0.18–21.29	0.59

CI indicates confidence interval, and HR, hazard ratio.
*Total number of events/total patient-months×100.
†Risk was estimated as an odds ratio from a logistic regression with 0.5 added to each group.

Stefan H. Hohnloser et al. Circ Arrhythm Electrophysiol. 2014;7:1019-1025.

Significant effect of digoxin use on the hazard of dronedarone for fatal outcomes

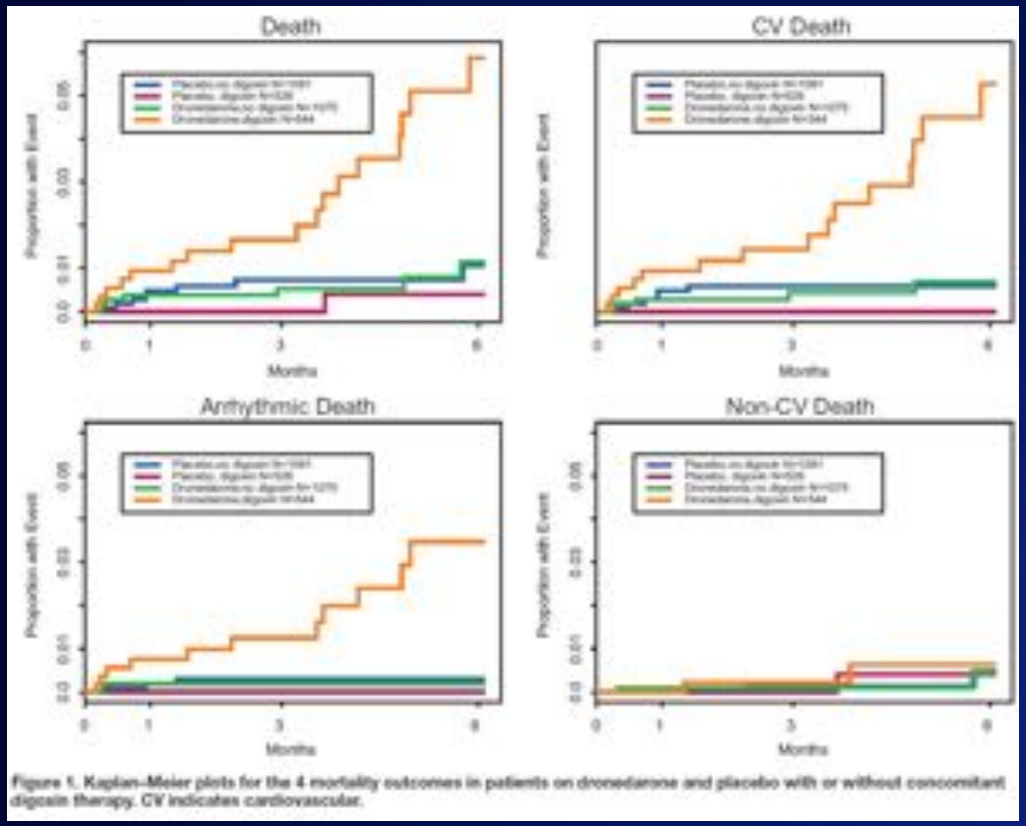


Figure 1. Kaplan–Meier plots for the 4 mortality outcomes in patients on dronedarone and placebo with or without concomitant digoxin therapy. CV indicates cardiovascular.

The significant dronedarone–digoxin interaction related to mortality persisted unchanged after adjustment for differences in baseline variables.

No effect of digoxin use on the hazard of dronedarone for heart failure

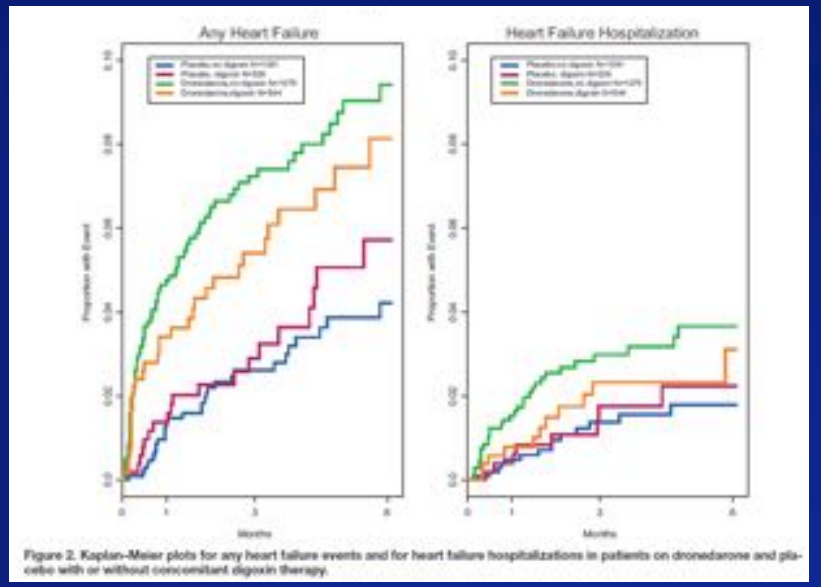


Figure 2. Kaplan–Meier plots for any heart failure events and for heart failure hospitalizations in patients on dronedarone and placebo with or without concomitant digoxin therapy.

Stefan H. Hohnloser et al. ***Circ Arrhythm Electrophysiol. 2014;7:1019-1025.***

LIMITATIONS

- **Digoxin therapy was not randomized**
- **<u>IT IS POSSIBLE THAT DIGOXIN USE IS MERELY A MARKER FOR HIGHER RISK PATIENTS</u> who would be more likely to display the adverse effects of dronedarone**
- In support of this argument is the fact that **<u>PATIENTS ON DIGOXIN</u>** were **<u>OLDER</u>** and, in general, **<u>SICKER</u>** than other patients

IN FAVOR of the observed interaction being a direct effect of digoxin is the fact that we observed **<u>NO INTERACTION RELATED TO COMBINED USE OF DIGOXIN AND DRONEDARONE RELATED TO HEART FAILURE</u>**

The specificity of the observed interaction for mortality, specifically arrhythmic death, together with the known potential for digoxin toxicity to cause serious brady- and tachyarrhythmias, suggests that the observed interaction is indeed directly related to digoxin

Stefan H. Hohnloser et al. Circ Arrhythm Electrophysiol. 2014;7:1019-1025.

WHAT IS THE UNDERLYING MECHANISM?

1) Increased digoxin itself is the driver of increased mortality in patients receiving dronedarone

Higher serum digoxin concentrations were significantly associated with all-cause mortality rates with particularly high mortality among subjects with serum digoxin concentrations ≥1.2 ng/mL (the DIG trial).

Dronedarone increased serum digoxin concentration in PALLAS patients to a mean concentration of 1.2 ng/mL, a level well above the range recommended by the DIG study post hoc analysis.

Despite these precautions, 6 of 8 serum digoxin concentrations available at day 7 in patients who suffered from
arrhythmic death in PALLAS were ≥1.2 ng/mL.

2) Dronedarone increases arrhythmic death but only in patients on digoxin unique toxicity

The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–533
Stefan H. Hohnloser et al. Circ Arrhythm Electrophysiol. 2014;7:1019-1025.

What remains unexplained…

Table 2. Study Outcomes.*

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI)†	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–3.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046
From arrhythmia	13	2.5	4	0.8	3.26 (1.06–10.0)	0.03
Stroke						
Any‡	23	4.4	10	1.9	2.32 (1.11–4.88)	0.02
Ischemic	18	3.4	9	1.7	2.01 (0.90–4.48)	0.08
Systemic embolism	1	0.2	0	0.0	NA	NA
Myocardial infarction or unstable angina	15	2.9	8	1.5	1.89 (0.80–4.45)	0.14
Myocardial infarction	3	0.6	2	0.4	1.54 (0.26–9.21)	0.63
Unplanned hospitalization for cardiovascular causes	113	22.5	59	11.4	1.97 (1.44–2.70)	<0.001
Hospitalization for heart failure	43	8.3	24	4.6	1.81 (1.10–2.99)	0.02
Heart-failure episode or hospitalization§	115	23.2	55	10.7	2.16 (1.57–2.98)	<0.001

…increased risk of heart failure seen with dronedarone in PALLAS

Stefan H. Hohnloser et al. Circ Arrhythm Electrophysiol. 2014;7:1019-1025.

Dronedarone and digitalis: individually reduced post-repolarization refractoriness enhances life-threatening arrhythmias.

Frommeyer G[1], Milberg P[2], Schulze Grotthoff J[2], Dechering DG[2], Kochhäuser S[2], Stypmann J[3], Fehr M[4], Breithardt G[2], Eckardt L[2].

The aim of this study was to assess possible proarrhythmic effects of dronedarone in combination with digitalis in an *experimental whole heart model*.

In this study, ouabain treatment resulted in an increased ventricular vulnerability
in chronically dronedarone pretreated control and failing hearts.

Ouabain led to a significant abbreviation of ventricular repolarization.

This was more marked in dronedarone pretreated hearts and resulted in an elevated incidence of VF.

This may help to interpret the results of the PALLAS trial

Frommeyer G et al. Europace. 2015 Aug;17(8):13008

Digoxin-associated mortality: a systematic review and meta-analysis of the literature

2015

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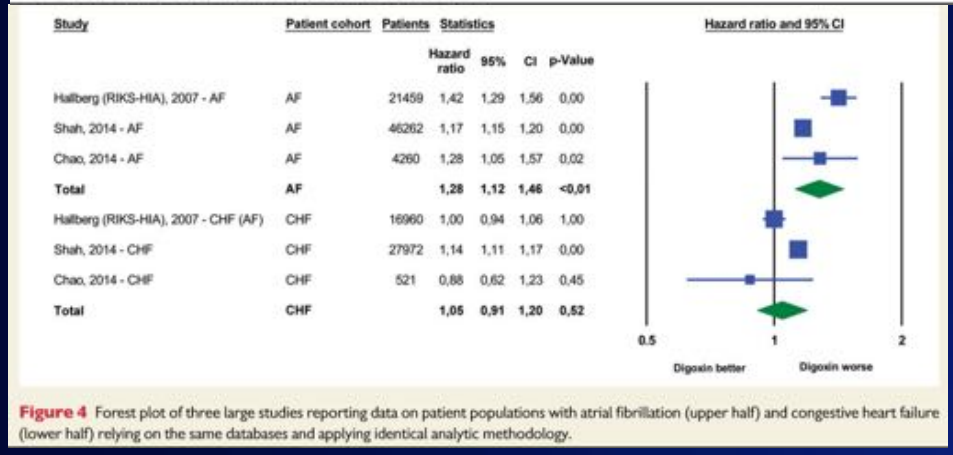

Study	Patient cohort	Patients	Statistics			
			Hazard ratio	95%	CI	p-Value
Hallberg (RIKS-HIA), 2007 - AF	AF	21459	1,42	1,29	1,56	0,00
Shah, 2014 - AF	AF	46262	1,17	1,15	1,20	0,00
Chao, 2014 - AF	AF	4260	1,28	1,05	1,57	0,02
Total	**AF**		**1,28**	**1,12**	**1,46**	**<0,01**
Hallberg (RIKS-HIA), 2007 - CHF (AF)	CHF	16960	1,00	0,94	1,06	1,00
Shah, 2014 - CHF	CHF	27972	1,14	1,11	1,17	0,00
Chao, 2014 - CHF	CHF	521	0,88	0,62	1,23	0,45
Total	**CHF**		**1,05**	**0,91**	**1,20**	**0,52**

Figure 4 Forest plot of three large studies reporting data on patient populations with atrial fibrillation (upper half) and congestive heart failure (lower half) relying on the same databases and applying identical analytic methodology.

2015

Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data

Oliver J Ziff,[1,2] Deirdre A Lane,[1,2] Monica Samra,[2] Michael Griffith,[3] Paulus Kirchhof,[1,3] Gregory Y H Lip,[1,2] Richard P Steeds,[4] Jonathan Townend,[1,4] Dipak Kotecha[1,2,4,5]

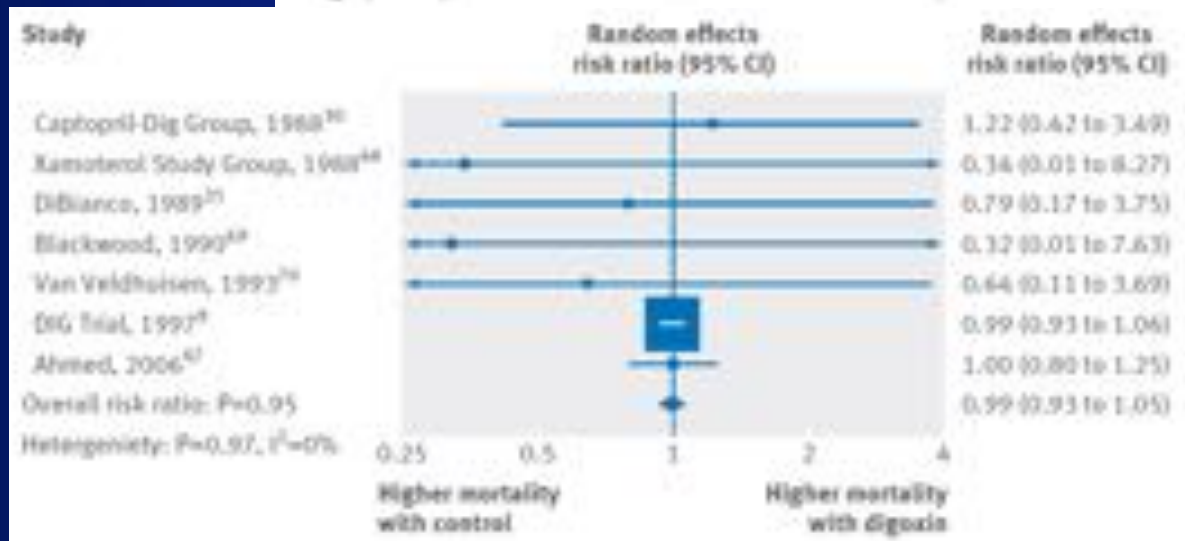

Fig 4 | Meta-analyses of all cause mortality in randomised controlled trials on safety and efficacy of digoxin

(*)Digoxin-associated mortality: asystematic review and meta-analysis of the literature. MateVamos, Julia W. Erath, and Stefan H.Hohnloser
(**) BMJ 2105;351:h4451

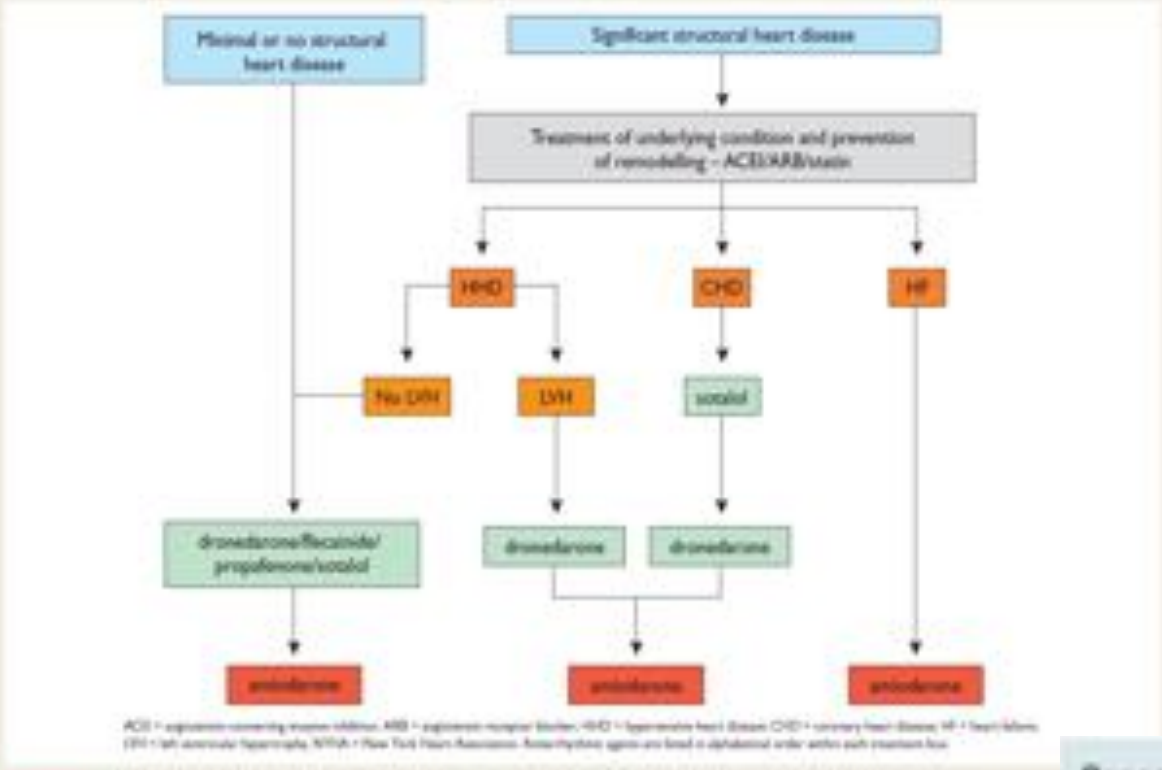

Figure 4 Choice of antiarrhythmic drug according to underlying pathology

Recommendations for oral antiarrhythmic agents

Recommendations	Class*	Level*	Ref*
Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm	I	A	142, 144, 153
Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients e.g. those at risk for therapy-associated complications.	IIb	B	145
Dronedarone is not recommended in patients with permanent AF	III	B	5

2012 focused update of the ESC Guidelines for the management of atrial fibrillation
European Heart Journal Nov 2012, 33 (21) 2719-2747

CONCLUSIONS

In ANDROMEDA and to a lesser extent in PALLAS, patients had more advanced cardiovascular disease and more comorbidities at enrolment than was seen in ATHENA patients

In the ANDROMEDA and PALLAS trials there was an increase in the rates of heart failure events or hospitalizations, which were clearly increased by dronedarone

The increased mortality in the ANDROMEDA trial was predominantly due to worsening heart failure without showing any increase in arrhythmic death

In contrast excess mortality in the PALLAS trial was attributed primarily to arrhythmic death and digoxin was present in the majority of those dead pts

Digoxin toxicity does not adequately explain the increased prevalence of stroke and heart failure seen in the PALLAS trial

The smaller trial ERATO had an even higher prevalence of Digoxin use (43%) without any observed increased mortality in the treatment arm but with a short follow up.

CONCLUSIONS

The difference in the prevalence of Digoxin use amongst the trials is insufficient to explain the diametric response to Dronedarone…

…hower the less-than-rigorous monitoring of serum levels of digoxin can lead to dangerous sequalae in clinical practice…

Thank you

for your

attention