Dronedarone in the Post-Pallas Era

Jorge E. Schliamser, MD

Carmel Medical Center

Haifa

Disclosures

None

Dronedarone is a multichannel blocker

- Dronedarone possesses electrophysiologic characteristics of all Four Vaughan Williams Classes as shown in animal models
  - Outward currents
    - Ikr: rapidly activating delayed rectifier potassium current
    - Iks: slowly activating delayed rectifier potassium current
    - Ito: transient outward current
    - Ik(Ach): muscarinic receptor-operated K+ current (atria)
  - Inward currents
    - Fast sodium currents
    - Calcium channel antagonist
- Dronedarone has anti-fibrillatory effects in the ventricles and atria

Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41(2):191-202.
Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-426.

Dronedarone possesses a different electrophysiological profile than amiodarone

	Guinea-pig (IC_{50}; μM)[1]	Dronedarone	Amiodarone
Outward currents	I_{Kr} (ventricle)	3	10
	I_{Ks} (ventricle)	10	30
	I_{K1} (ventricle)	>30	≤30
	$I_{K(Ach)}$ (atrium)*	0.01	1

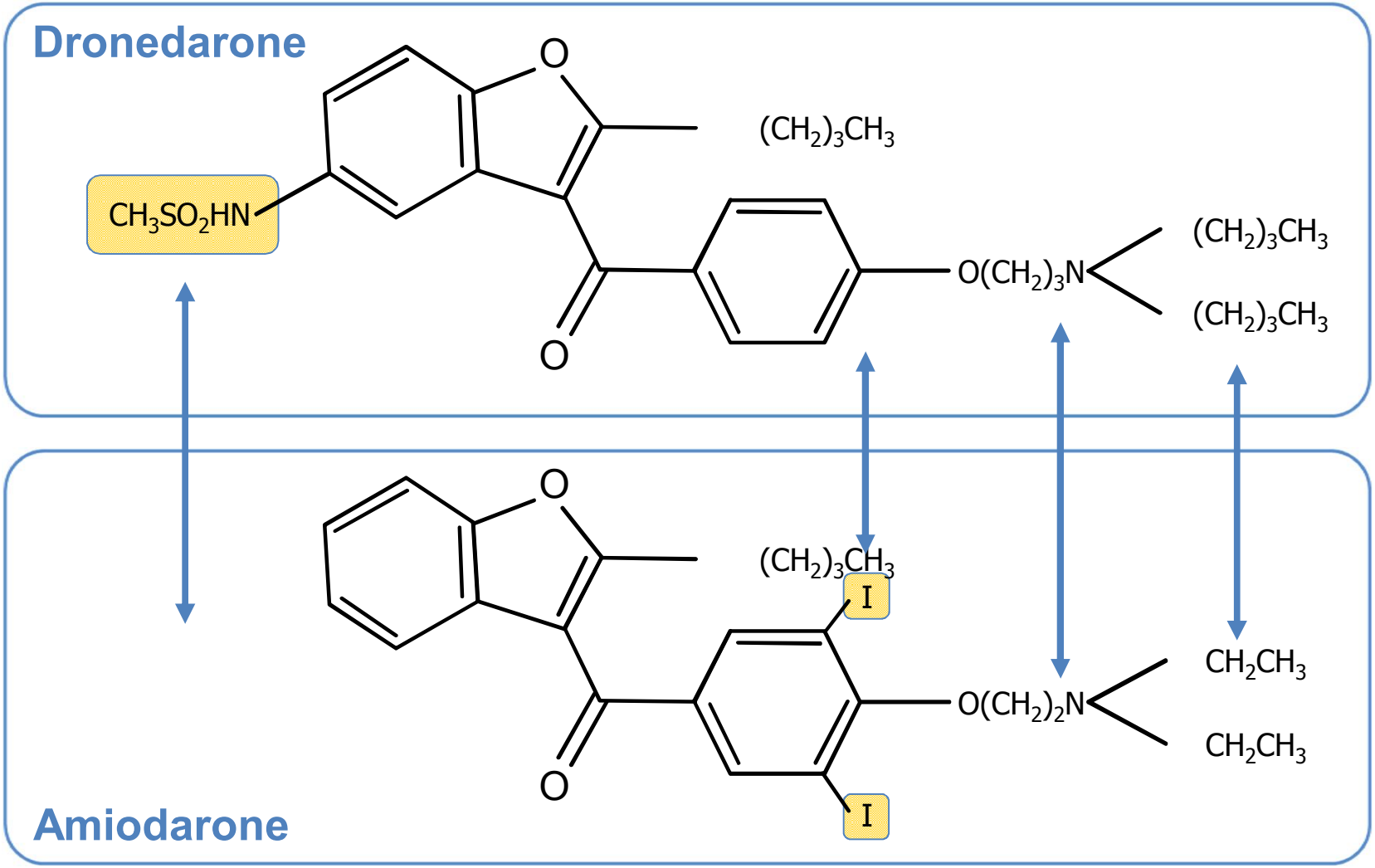
*I_{Ks}, I_{Kr}, I_{to}, I_{K1}, I_{KUR}

		Dronedarone	Amiodarone
Inward currents	I_{Na} (human; 3 μM)[2]	-97%	-41%
	$I_{Ca(L)}$ (guinea pig; CI_{50}, μM)[1]	0.2	10

Adapted from:

1. Lalevée N, *et al. J Cardiovasc Electrophysiol.* 2003;14:885-890.
2. Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41:191-202.

Dronedarone has structural differences compared to amiodarone



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

Dronedarone and amiodarone-Important pharmacological differences

Dronedarone	Amiodarone
Inhibit multiple K^+ channels	
Inhibit Na^+ and Ca^{2+} channels	
Exert anti-adrenergic effects	
Low proarrhythmic profile	
No significant effect on LV function	
No iodine	Iodine
Short half-life (25-30 hours) and no tissue accumulation	High lipophilicity with long half life (28-180 days) and tissue accumulation
Coronary vasodilation refractory to inhibition of NO synthase pathway	Coronary vasodilation highly dependent on NO
Dronedarone has a greater anti-hypertensive effect than amiodarone	

Adapted from:

Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41(2):191-202.
Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-426.
Kathofer *et al. Cardiovasc Drug Rev* 2005;23(3):217-30
Wegener F et al. J Cardiovasc Electrophysiol. 2006;17(S2):S17-S20
Guiraudou P, *et al. European Journal of Pharmacology* 2004;496:119-127.
Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010;21(6):597-605.

NO=Nitric oxide
LV=Left ventricular
BP=Blood pressure

Dronedarone-CV Properties

- Antiarrhythmic efficacy at atrial level
- Rate controlling effects
- Vasodilatory effects
- Anti-adrenergic effects
- Blood pressure lowering properties

Dronedarone Trials I

	DAFNE[1]	EURIDIS/ ADONIS[2]	ERATO[3]
Trial objective	Dose finding study	Effect of dronedarone on maintenance of sinus rhythm	Effect of dronedarone in the control of mean 24-hour ventricular rate
Patient population	Persistent AF	Paroxysmal/ Persistent AF	Permanent AF
Patient AF status at baseline	In AF but eligible for AAD treatment and cardioversion	In sinus rhythm	In permanent AF
Number of patients	102	1,237	174
Dronedarone Versus	Placebo	Placebo Both arms received standard therapy*	Placebo Both arms received standard therapy*
Primary endpoint	Time to first AF recurrence	Time to first AF/AFL recurrence	Change in mean ventricular rate measured by 24-hour Holter ECG on Day 14 compared to baseline

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and/or aspirin and other antiplatelet therapy) and/or other CV agents such as ACEIs/ARBs and statins

Adapted from:

1. Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.
2. Singh BN, *et al. N Engl J Med.* 2007;357:987-99.
3. Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

Dronedarone Trials II

	ATHENA[1]	DIONYSOS[2]	ANDROMEDA[3]	PALLAS[4]
Trial objective	Evaluate the efficacy and safety of dronedarone in the prevention of CV hospitalisation or all-cause death	Investigate efficacy and safety of dronedarone versus amiodarone for the maintenance of sinus rhythm	Evaluate the potential benefit of dronedarone on all cause death or hospitalisation for worsening heart failure	Evaluate the benefit of dronedarone in high risk permanent AF patients in reducing major CV events
Patient population	Paroxysmal/ Persistent AF	Persistent AF	Unstable recently decompensated CHF patients	Permanent AF
Patient AF status at baseline	In sinus rhythm or AF but eligible for cardioversion	In AF but eligible for AAD treatment and cardioversion	N/A	In permanent AF
Number of patients	4,628	504	627	3,236 (10,800 planned)
Dronedarone Versus	Placebo Both arms received standard therapy*	Amiodarone	Placebo	Placebo Both arms received standard therapy*
Primary endpoint	CV hospitalisation or all-cause mortality	Treatment failure defined as recurrence of AF OR premature study drug discontinuation for intolerance or lack of efficacy	Death from any cause or hospitalisation for worsening heart failure *Trial stopped early for safety reasons*	Stroke, myocardial infarction, systemic embolism or CV death *Trial stopped early for safety reasons*

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and/or aspirin and other antiplatelet therapy) and/or other CV agents such as ACEIs/ARBs and statins

Adapted from:

1. Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.
2. Le Heuzey JY *et al. J Cardiovasc Electrophysiol.* 2010;21(6):597-605.
3. Køber L, *et al. N Engl J Med.* 2008;358:2678-87.
4. Connolly SJ et al. N Engl J Med 2011; 365:2268-2276

Dronedarone: The most extensively studied antiarrhythmic drug in AF

10,676 patients, including 5,553 receiving dronedarone

Studies	N	Population	Objectives
DAFNE[1]	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS/ADONIS[2]	612/625	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ERATO[3]	174	Permanent AF	Ventricular rate control
DIONYSOS[4]	504	Persistent AF	Comparative trial vs amiodarone
ANDROMEDA[5†]	627 / 1,000*	Unstable CHF and LV dysfunction (25% in AF)	Morbidity-mortality study
ATHENA[6]	4628	Paroxysmal/ Persistent AF/AFL	Prevention of CV hospitalization or death
PALLAS[7]	3236 / 10,800*	Permanent AF	Prevention of major CV events/ hospitalization or death

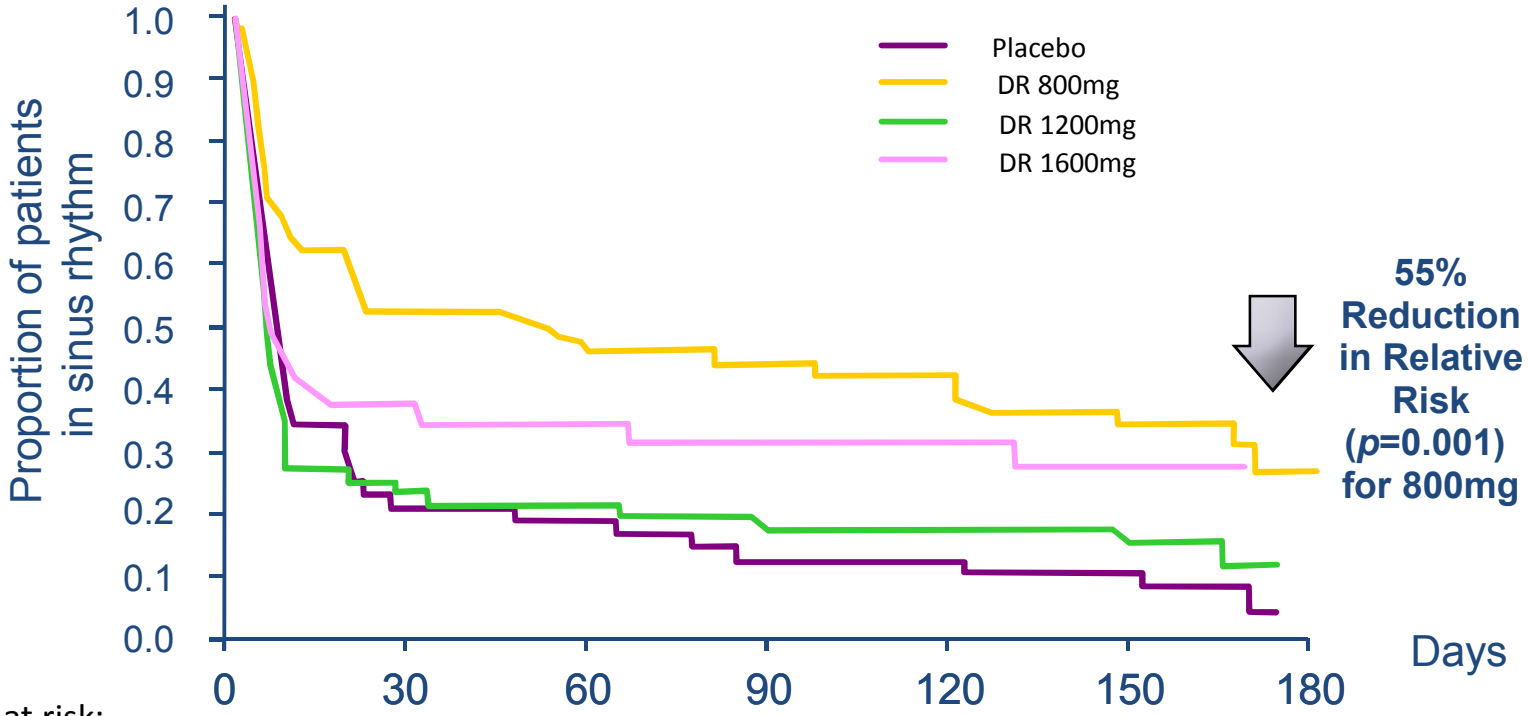
†Heart failure study
*Planned patient enrolment

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7. .1
Singh BN, *et al. N Engl J Med.* 2007;357:987-99. .2
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9. .3

Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010 Apr 6 Epub .4
Køber L, et al. N Engl J Med. 2008;358:2678-87. .5
Hohnloser SH, et al. N Engl J Med 2009;360:668-78 .6
Connolly SJ, et al. N Engl J Med 2011 .7

In patients initiated prior to cardioversion, dronedarone 400 mg bid significantly reduced the risk of AF recurrence by 55%

Persistent AF patients: Primary endpoint



Patients at risk:

Placebo	48	12	11	8	8	7	5
DR 800mg	54	29	26	25	24	21	18
DR 1200mg	54	14	13	12	11	11	9
DR 1600mg	43	15	12	11	11	9	8

Adapted from Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Dronedarone: The most extensively studied antiarrhythmic drug in AF

10,676 patients, including 5,553 receiving dronedarone

Studies	N	Population	Objectives
DAFNE[1]	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS/ADONIS[2]	612/625	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ERATO[3]	174	Permanent AF	Ventricular rate control
DIONYSOS[4]	504	Persistent AF	Comparative trial vs amiodarone
ANDROMEDA[5†]	627 / 1,000*	Unstable CHF and LV dysfunction (25% in AF)	Morbidity-mortality study
ATHENA[6]	4628	Paroxysmal/ Persistent AF/AFL	Prevention of CV hospitalization or death
PALLAS[7]	3236 / 10,800*	Permanent AF	Prevention of major CV events/ hospitalization or death

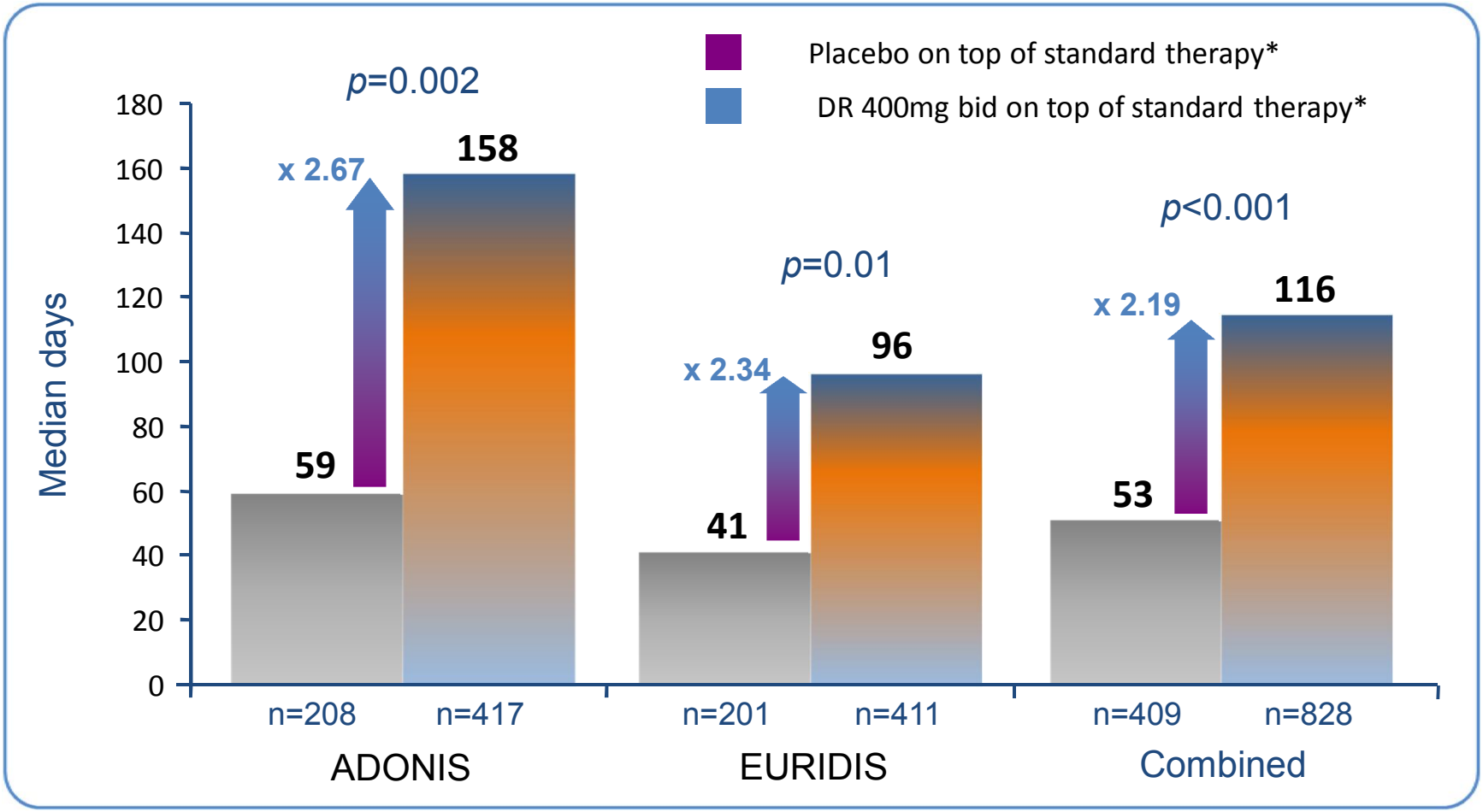
†Heart failure study
*Planned patient enrolment

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7. .1
Singh BN, *et al. N Engl J Med.* 2007;357:987-99. .2
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9. .3

Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010 Apr 6 Epub .4
Køber L, et al. N Engl J Med. 2008;358:2678-87. .5
Hohnloser SH, et al. N Engl J Med 2009;360:668-78 .6
Connolly SJ, et al. N Engl J Med 2011 .7

Dronedarone more than doubled time to first AF/AFL recurrence

Paroxysmal/persistent AF patients: Primary endpoint



*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other CV therapy such as ACE inhibitors and statins

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

Dronedarone: The most extensively studied antiarrhythmic drug in AF

10,676 patients, including 5,553 receiving dronedarone

Studies	N	Population	Objectives
DAFNE[1]	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS/ADONIS[2]	612/625	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ERATO[3]	174	Permanent AF	Ventricular rate control
DIONYSOS[4]	504	Persistent AF	Comparative trial vs amiodarone
ANDROMEDA[5†]	627 / 1,000*	Unstable CHF and LV dysfunction (25% in AF)	Morbidity-mortality study
ATHENA[6]	4628	Paroxysmal/ Persistent AF/AFL	Prevention of CV hospitalization or death
PALLAS[7]	3236 / 10,800*	Permanent AF	Prevention of major CV events/ hospitalization or death

†Heart failure study
*Planned patient enrolment

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7. .1
Singh BN, *et al. N Engl J Med.* 2007;357:987-99. .2
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9. .3

Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010 Apr 6 Epub .4
Køber L, et al. N Engl J Med. 2008;358:2678-87. .5
Hohnloser SH, et al. N Engl J Med 2009;360:668-78 .6
Connolly SJ, et al. N Engl J Med 2011 .7

- ANDROMEDA (**AN**tiarrhythmic trial with **DRO**nedarone in **M**oderate to severe CHF **E**valuating morbidity **D**ecre**A**se) was:
  - Conducted in high-risk congestive heart failure (CHF) patients with left ventricular dysfunction and a recent acute decompensation
  - Aimed to evaluate the potential benefit of dronedarone on all cause death or hospitalisation for worsening heart failure

- Patients were not selected based on AF / AFL history

Adapted from Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Study endpoints

- Primary endpoint
  - Death from any cause or hospitalisation for worsening heart failure

- Secondary endpoints
  - Death from all causes
  - Hospitalisation for cardiovascular causes
  - Hospitalisation for worsening heart failure
  - Occurrence of atrial fibrillation or flutter
  - Death from arrhythmia
  - Sudden death

Adapted from Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

In ANDROMEDA, patients were not selected based on history of AF/AFL

	Placebo n=317	Dronedarone 400mg bid n=310
Age (years) Median (range)	72 (27-96)	71 (33-90)
Weight (kg)	79	78
Gender [n (%)] Male	242 (76.3%)	230 (74.2%)
Wall motion index (WMI)		
Median (range)	0.9 (0.3-1.2)	0.9 (0.3-1.2)
NYHA class [n (%)]		
Class II	121 (38.2%)	131 (42.3%)
Class III	183 (57.7%)	173 (55.8%)
Class IV	13 (4.1%)	6 (1.9%)
Mean duration of heart failure (mo)	23	20
Estimated GFR (ml/min)		
Mean (range)	52.8 (6-99)	50 (16-104)
Atrial fibrillation or flutter mean (%)	85 (26.8)	72 (23.2)

WMI=Wall-Motion Index.

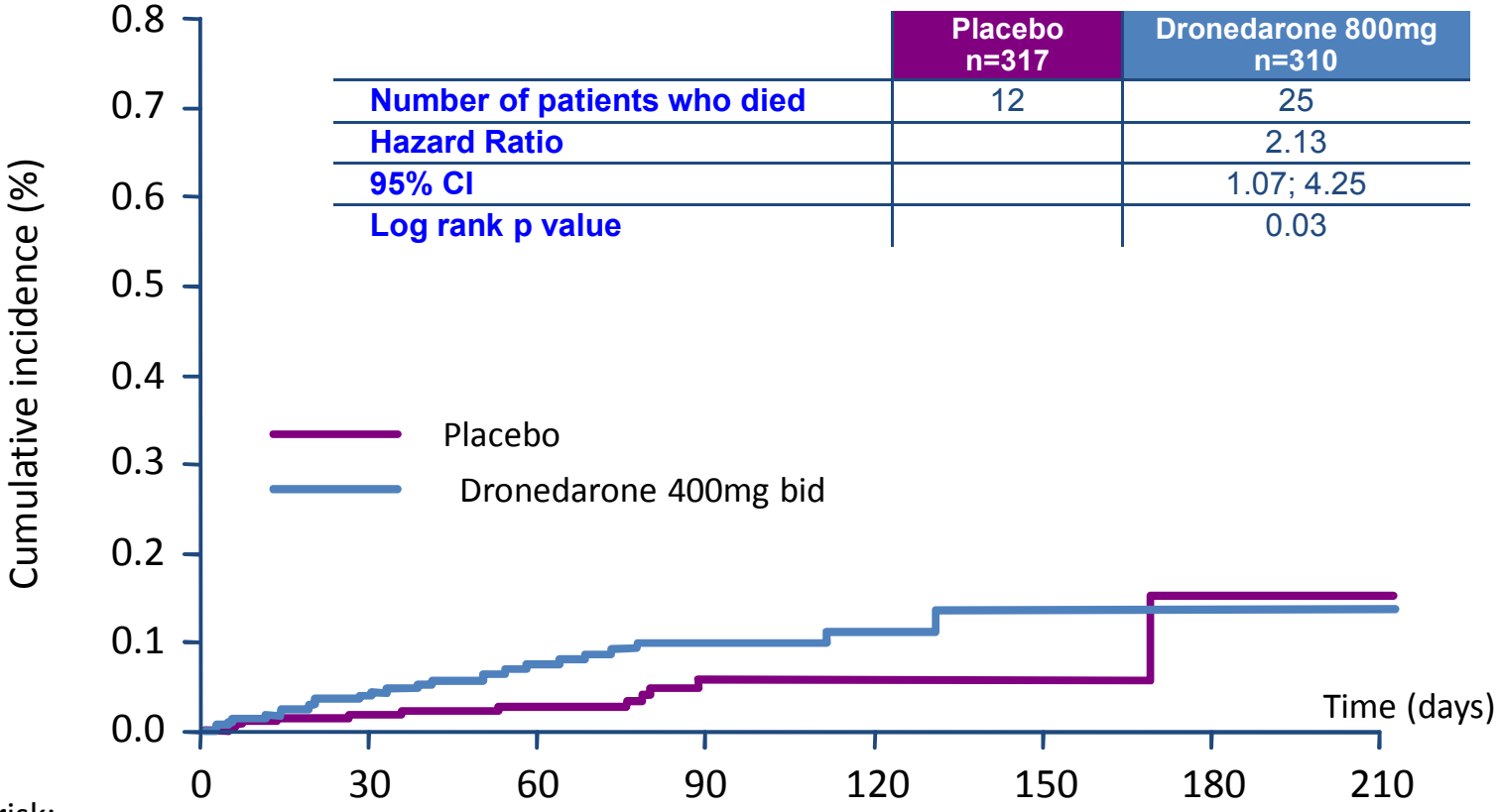
Adapted from Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA

Increase in all-cause mortality in unstable CHF patients

Secondary endpoint

	Placebo n=317	Dronedarone 800mg n=310
Number of patients who died	12	25
Hazard Ratio		2.13
95% CI		1.07; 4.25
Log rank p value		0.03



Patients at risk:

Placebo	317	256	181	103	50	18	6	1
DR 400mg bid	310	257	174	104	59	22	5	1

Adapted from Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA – Key points

- ANDROMEDA was conducted in unstable CHF patients most of whom did not even have AF
- Dronedarone did not reduce mortality or decrease CV hospitalisations vs. placebo
- There was an increase in non-sudden cardiac deaths related to worsening heart failure
- No significant difference between placebo and dronedarone patients was seen for arrhythmic events and sudden deaths

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Dronedarone: The most extensively studied antiarrhythmic drug in AF

10,676 patients, including 5,553 receiving dronedarone

Studies	N	Population	Objectives
DAFNE[1]	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS/ADONIS[2]	612/625	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ERATO[3]	174	Permanent AF	Ventricular rate control
DIONYSOS[4]	504	Persistent AF	Comparative trial vs amiodarone
ANDROMEDA[5†]	627 / 1,000*	Unstable CHF and LV dysfunction (25% in AF)	Morbidity-mortality study
ATHENA[6]	4628	Paroxysmal/ Persistent AF/AFL	Prevention of CV hospitalization or death
PALLAS[7]	3236 / 10,800*	Permanent AF	Prevention of major CV events/ hospitalization or death

†Heart failure study
*Planned patient enrolment

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7. .1
Singh BN, *et al. N Engl J Med.* 2007;357:987-99. .2
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9. .3

Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010 Apr 6 Epub .4
Køber L, et al. N Engl J Med. 2008;358:2678-87. .5
Hohnloser SH, et al. N Engl J Med 2009;360:668-78 .6
Connolly SJ, et al. N Engl J Med 2011 .7

ATHENA Trial

(**A** placebo-controlled, double-blind, parallel arm **T**rial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular **H**ospitalization or death from any cause in pati**EN**ts with **A**trial fibrillation/atrial flutter)

ATHENA Trial: Study Design

4,628 patients ≥75 years with atrial fibrillation or 70-75 years with atrial fibrillation and at least one additional cardiovascular risk factor prior to randomization.
Double blind. Randomized. Placebo controlled. International multicenter. Mean follow-up 21 months.

R

Dronedarone 400 mg BID	Placebo

12-30 mos. follow-up

- Primary Endpoint: composite of all-cause mortality combined with cardiovascular hospitalization
- Secondary Endpoint: death from any cause, cardiovascular death, hospitalization for cardiovascular reasons

JCE 2008; 19.1/Heart Rhythm 2008

ATHENA Trial: Inclusion Criteria

- ≥75 yrs with or without additional risk factors

- ≥70 yrs with at least one of the following risk factors: arterial hypertension (ongoing therapy with at least two antihypertensive drugs of different classes), diabetes mellitus, prior stroke or transient ischemic attack or systemic embolism, left atrium diameter ≥ 50 mm by M-mode echocardiography, LVEF < 0.40 by 2D-echocardiography.

JCE 2008; 19.1/Heart Rhythm 2008

ATHENA Trial: Exclusion Criteria

Presence of one of the following cardiac conditions:

- Permanent AF
- Unstable hemodynamic situation (i.e., recently decompensated heart failure)
- Congestive heart failure NYHA class IV
- Planned major non-cardiac or cardiac surgery
- Acute myocarditis
- Bradycardia < 50 bpm and/or a PR interval > 0.28 seconds
- Significant sinus node disease in the past, if not treated with a pacemaker

JCE 2008; 19.1/Heart Rhythm 2008

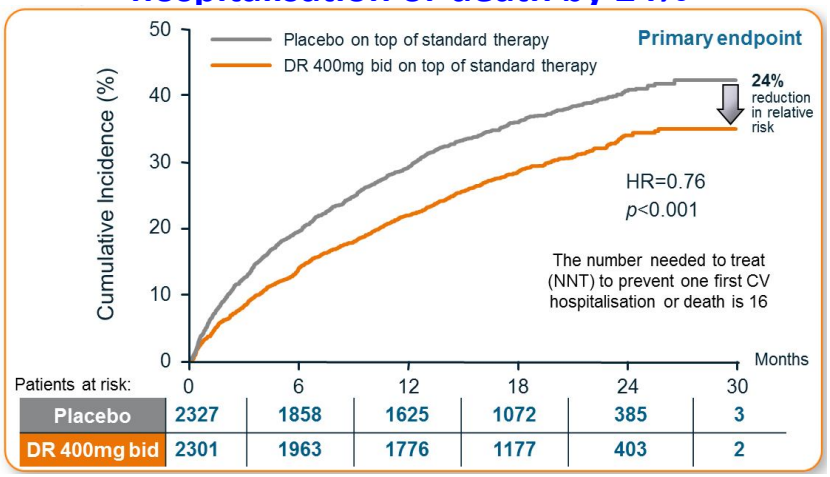
Athena-Baseline Characteristics

	Placebo n=2,327	Dronedarone n=2,301	All patients n=4,628
Age (mean ±SD, years)	71.7 ±9.0	71.6 ±8.9	72 ±9.0
<65yr	442 (19.0%)	431 (18.7%)	873 (18.9%)
65 to 75yr	907 (39.0%)	923 (40.1%)	1,830 (39.5%)
≥75yr	978 (42.0%)	947 (41.2%)	1,925 (41.6%)
Female gender	1,038 (44.6%)	1,131 (49.2%)	2,169 (46.9%)
AF/AFL at baseline	586 (25.2%)	569 (24.7%)	1,155 (25.0%)
Structural heart disease	1,402 (60.9%)	1,330 (58.3%)	2,732 (59.6%)
Hypertension	1,996 (85.8%)	1,999 (86.9%)	3,995 (86.3%)
Coronary heart disease	737 (31.7%)	668 (29.0%)	1,405 (30.4%)
Valvular heart disease	380 (16.3%)	379 (16.5%)	759 (16.4%)
Non-ischemic cardiomyopathy	131 (5.6%)	123 (5.3%)	254 (5.5%)
History of CHF NYHA II/III	515 (22.1%)	464 (20.2%)	979 (21.2%)
LVEF <0.45	285/2,281 (12.5%)	255/2,263 (11.3%)	540/4,544 (11.9%)
LVEF <0.35	87/2,281 (3.8%)	92/2,263 (4.1%)	179/4,544 (3.9%)
Lone atrial fibrillation	139 (6.0%)	140 (6.1%)	279 (6.0%)
Pacemaker	243 (10.4%)	214 (9.3%)	457 (9.9%)

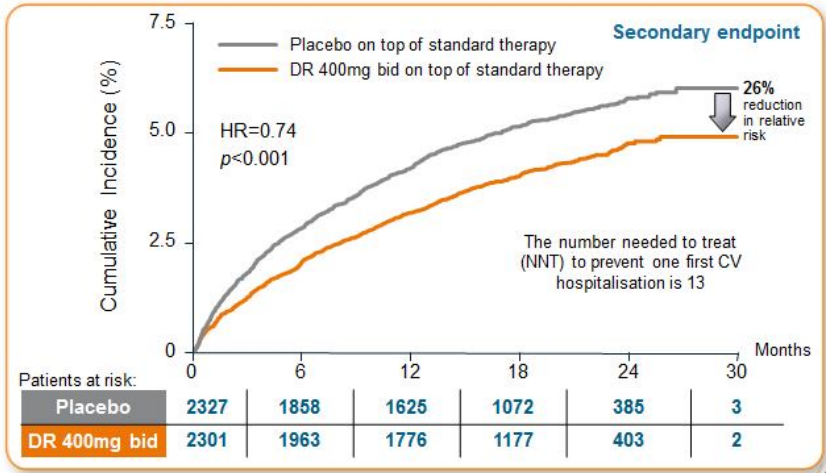
Adapted from Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

In ATHENA, dronedarone decreased…

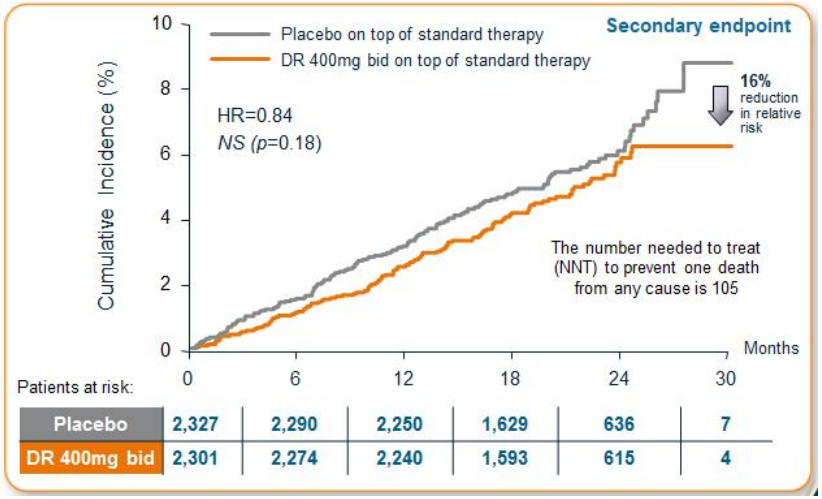
…significantly the risk of unplanned CV hospitalisation or death by 24%



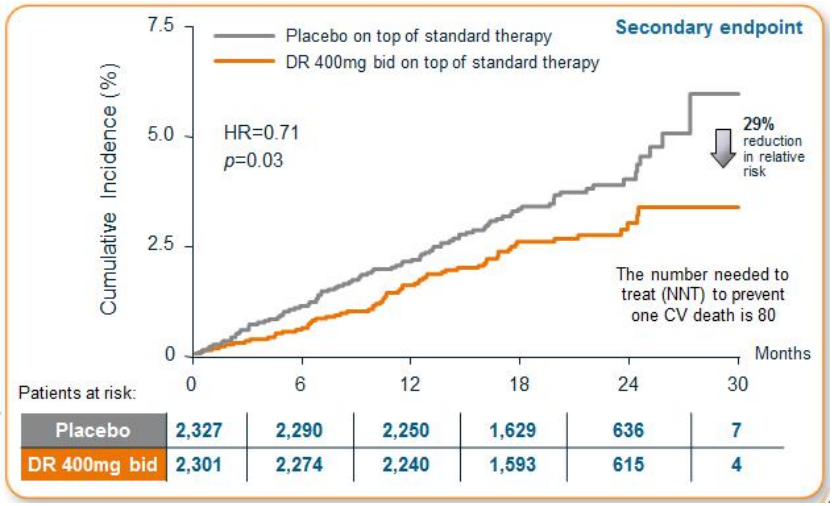
…significantly the risk of unplanned hospitalisation by 26%



…the risk of all-cause death by 16%



…significantly the risk of CV death by 29%



Mean follow-up 21 ±5 months.

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

Athena Trial Results

- 24% significant risk reduction in the combined endpoint of CV hospitalisation or death
- 29% significant risk reduction in CV death
- 16% trend to lower risk of death from any cause
- 45% significant risk reduction for arrhythmic death (sudden death)
- 34% significant risk reduction for stroke (sub analysis)
- 26% significant risk reduction in CV hospitalisation

Dronedarone: The most extensively studied antiarrhythmic drug in AF

10,676 patients, including 5,553 receiving dronedarone

Studies	N	Population	Objectives
DAFNE[1]	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS/ADONIS[2]	612/625	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ERATO[3]	174	Permanent AF	Ventricular rate control
DIONYSOS[4]	504	Persistent AF	Comparative trial vs amiodarone
ANDROMEDA[5†]	627 / 1,000*	Unstable CHF and LV dysfunction (25% in AF)	Morbidity-mortality study
ATHENA[6]	4628	Paroxysmal/ Persistent AF/AFL	Prevention of CV hospitalization or death
PALLAS[7]	3236 / 10,800*	Permanent AF	Prevention of major CV events/ hospitalization or death

Dronedarone is contraindicated in permanent AF and should not be used for rate control

†Heart failure study
*Planned patient enrolment

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7. .1
Singh BN, *et al. N Engl J Med.* 2007;357:987-99. .2
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9. .3
Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010 Apr 6 Epub .4
Køber L, et al. N Engl J Med. 2008;358:2678-87. .5
Hohnloser SH, et al. N Engl J Med 2009;360:668-78 .6
Connolly SJ, et al. N Engl J Med 2011 .7

The NEW ENGLAND JOURNAL of MEDICINE

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., Álvaro 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 Delacrétaz, 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

Permanent Atrial Fibri**LLA**tion Outcome **S**tudy using Dronedarone on Top of Standard Therapy

http://clinicaltrials.gov Number: NCT01151137

30

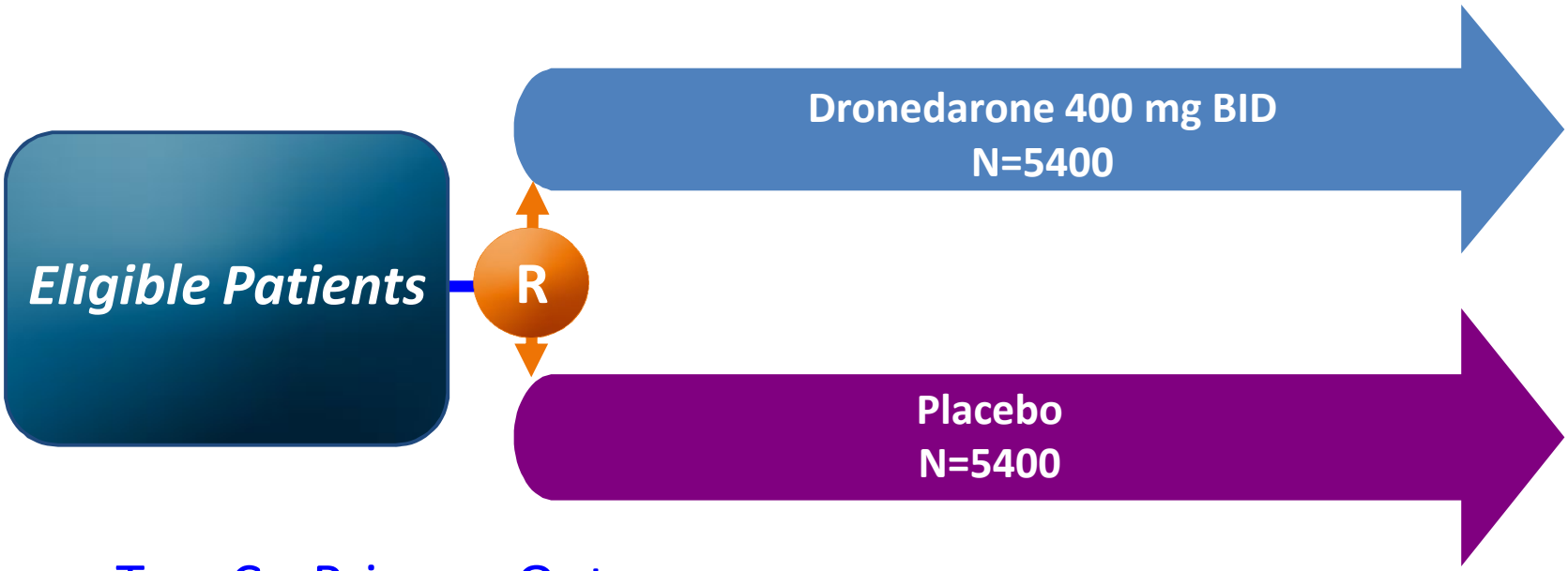
Background

- In paroxysmal and persistent AF, dronedarone reduced AF recurrence; and reduced the combined outcome of cardiovascular hospitalization or death in ATHENA
  - It also reduced cardiovascular death, stroke and arrhythmic death
- Dronedarone has other potentially beneficial effects
  - Heart rate slowing in AF
  - BP lowering
  - Anti-adrenergic effects
  - Anti-ventricular arrhythmia effects
- Hypothesis: dronedarone would reduce major vascular events in permanent AF

PALLAS Patient Inclusion / Exclusion

- **Inclusion criteria**
  - **Permanent AF**
    - Atrial fibrillation or flutter, present for at least 6 months
  - **Age ≥ 65 years**
  - **Major Risk factor (at least one)**
    - History of either coronary artery or peripheral arterial disease
    - History of stroke or TIA
    - Heart failure hospitalization in past year, or LVEF≤ 40%
    - Age ≥ 75 years, with both hypertension and diabetes mellitus
- **Major exclusion criteria**
  - Severe heart failure symptoms (NYHA class IV) or recent unstable NYHA class III
  - Bradycardia < 50 bpm or QTc interval > 500 ms without pacemaker
  - Implantable cardioverter-defibrillator

PALLAS Design



- Two Co-Primary Outcomes
  1. Stroke, myocardial infarction, systemic embolism or cardiovascular death
  2. Unplanned cardiovascular hospitalization or death

- Planned study enrolment of 10,800 patients
- Two years of recruitment and one final year of follow up
- 844 first co-primary outcome events

Baseline Characteristics

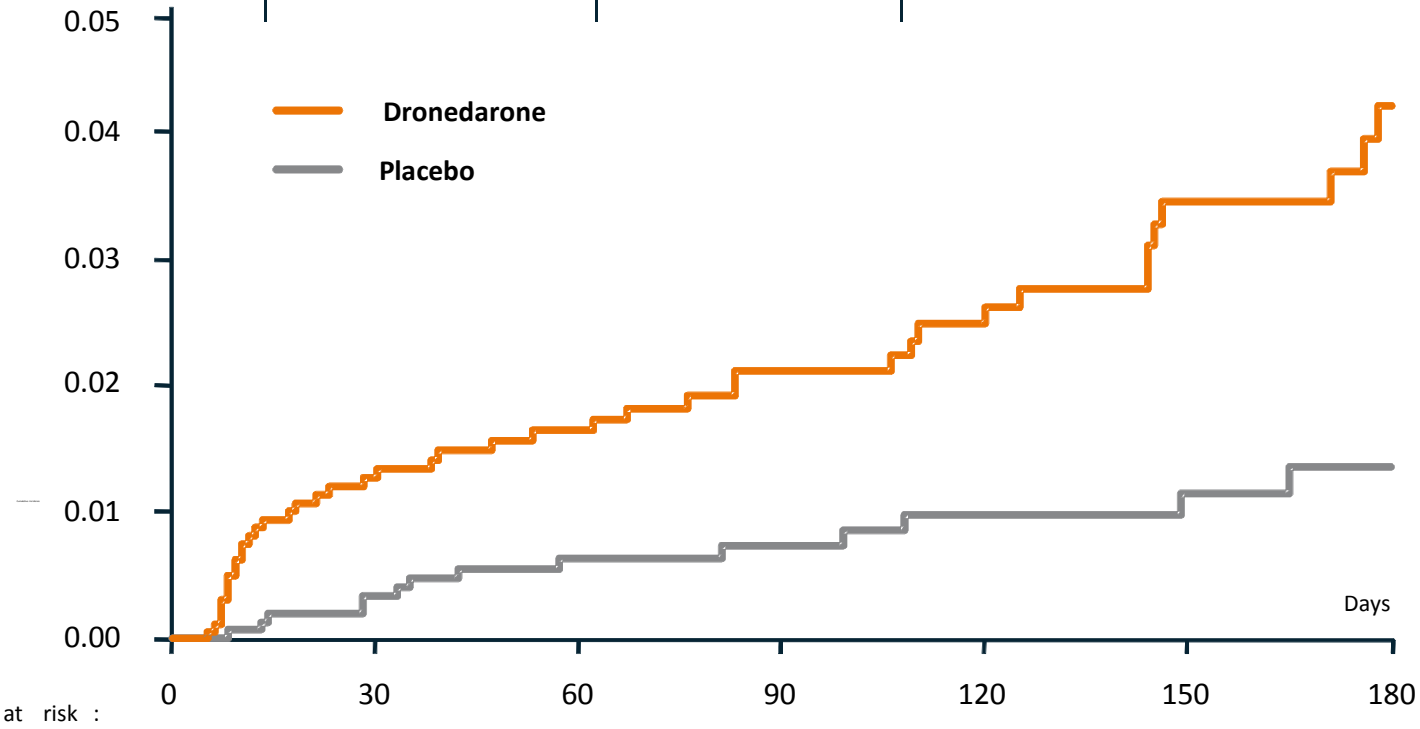
	Dronedarone N=1619	Placebo N=1617
Age years mean (SD)	75.0 (5.9)	75.0 (5.9)
Duration of permanent AF > 2 years	1119 (69.1%)	1124 (69.5%)
Coronary artery disease	661 (40.8%)	666 (41.2%)
Peripheral arterial disease	187 (11.6%)	213 (13.2%)
Prior Stroke or TIA	436 (26.9%)	458 (28.3%)
History of heart failure	1139 (70.4%)	1117 (69.1%)
Left ventricular ejection fraction ≤ 40%	345 (21.3%)	335 (20.7%)
Baseline use of a Beta-blocker	1201 (74%)	1201 (74%)
Baseline use of Vitamin K antagonist	1359 (84%)	1363 (84%)

Early Termination of PALLAS

- First patient enrolled on July 19, 2010
- Data monitoring Committee recommended study termination for safety on July 5, 2011
- 3,236 Patients randomized
  - from 489 sites in 37 countries
  - 3.5 months median follow-up

Stroke, systemic embolism, myocardial infarction or cardiovascular death

First Co-primary Outcome	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	43 (2.7%)	19 (1.2%)	2.29 (1.34 – 3.94) p=0.002

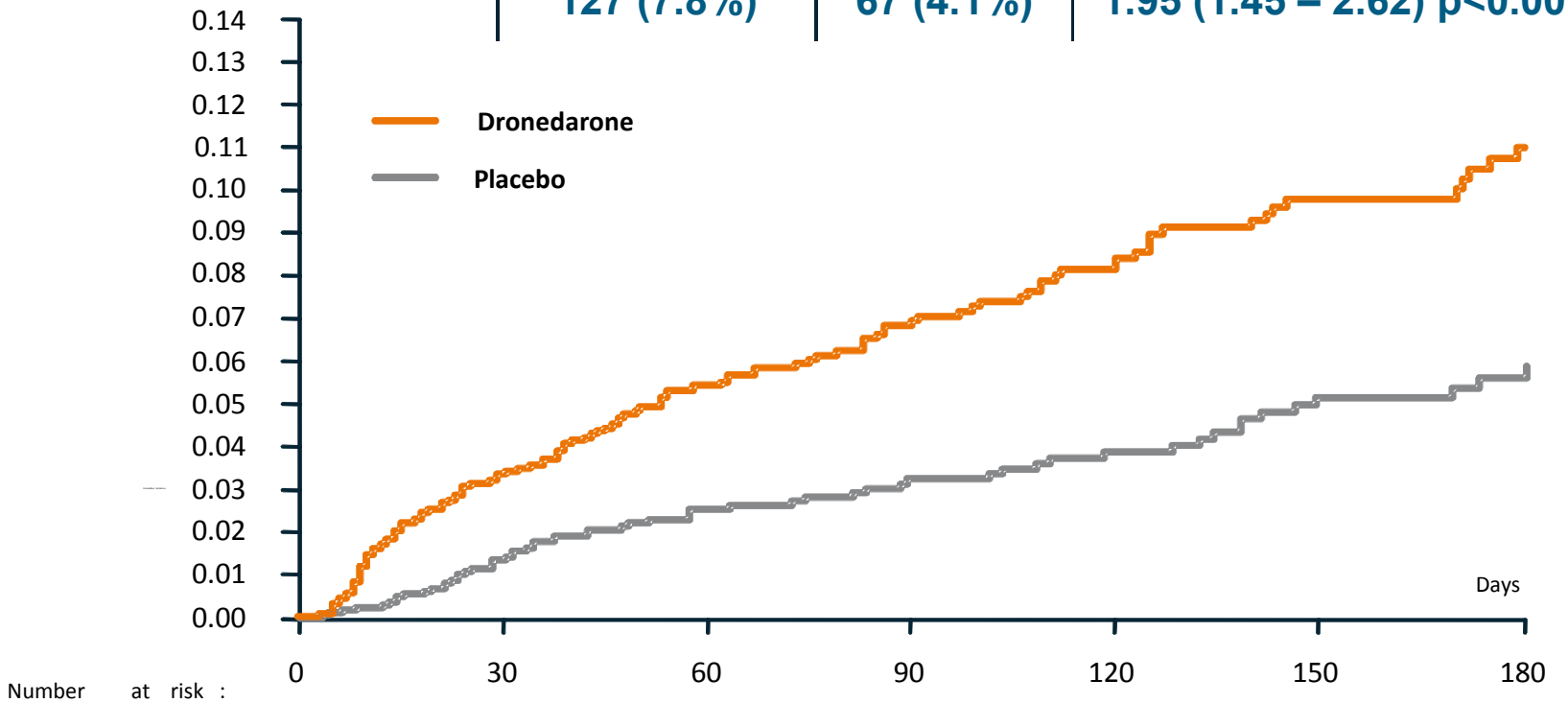


Number at risk :

Dronedarone	1619	1421	930	353
Placebo	1617	1445	908	377

Unplanned cardiovascular hospitalization or death

Second Co-primary Outcome	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	127 (7.8%)	67 (4.1%)	1.95 (1.45 – 2.62) p<0.001



Number at risk :

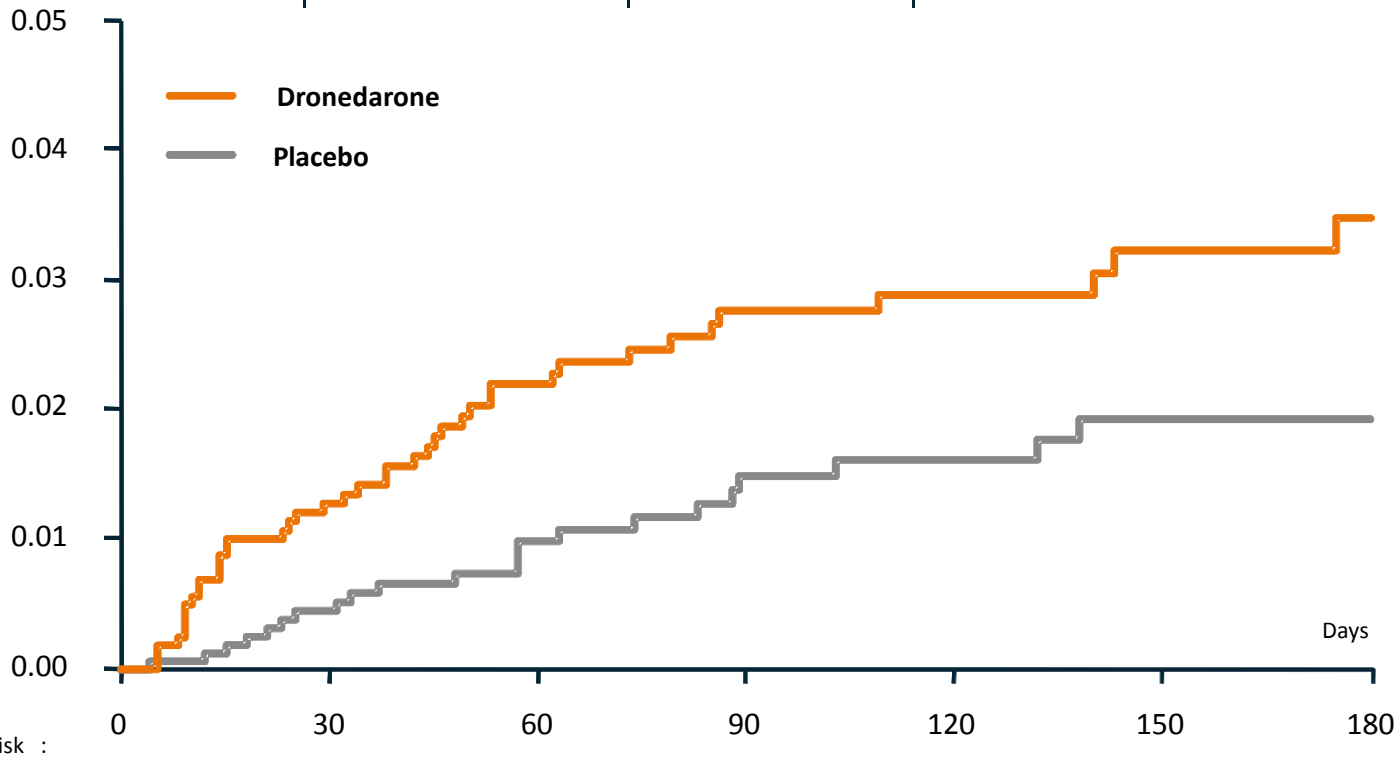
Dronedarone	1619	1389	879	334
Placebo	1617	1429	882	361

Components of the Primary Outcomes

	Dronedarone N=1619	Placebo N=1617	HR 95% CI, p-value
Death	25	13	1.94 [0.99- 3.79] p=0.049
Cardiovascular Death	21	10	2.11 [1.00- 4.49], p=0.046
Arrhythmic Death	13	4	3.26 [1.06- 10.0], p=0.03
Stroke	23	10	2.32 [1.11- 4.88], p=0.02
Myocardial Infarction	3	2	1.54 [0.26- 9.21], p=0.63
Unplanned CV Hospitalization	113	59	1.97 [1.44- 2.70], p<0.001
Heart Failure Hospitalization	43	24	1.81 [1.10-2.99], p=0.02

Heart Failure Hospitalization

Heart Failure Hospitalization	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	43 (2.7%)	24 (1.5%)	1.81 (1.10 – 2.99) p=0.02

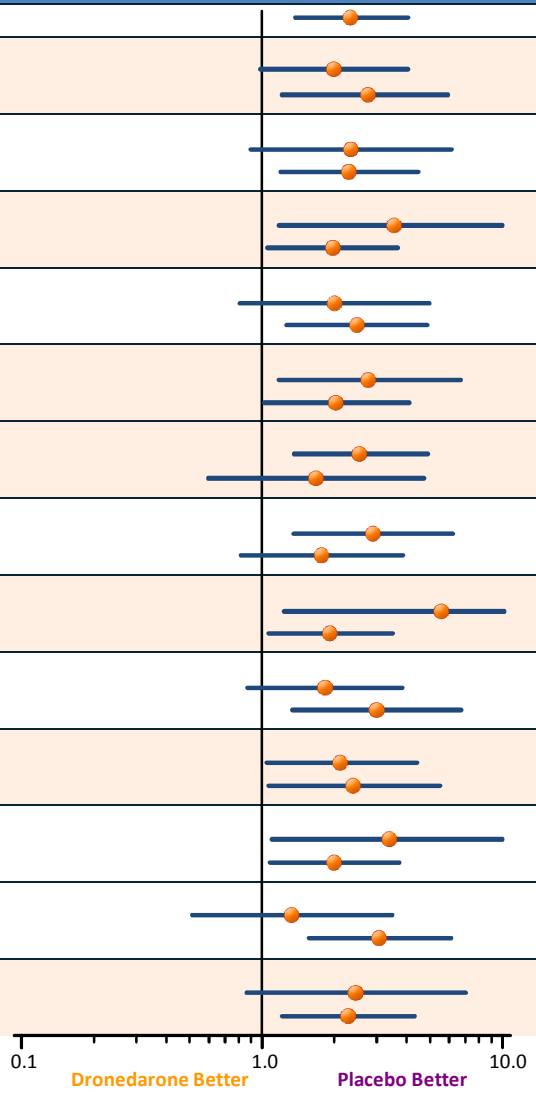


Number at risk :

Dronedarone	1619	1414	912	349
Placebo	1617	1439	896	374

Sub-groups: First Co-primary Outcome

Charateristics	N	HR [95% CI]	P value[b]
Overall		2.29 [1.34;3.94]	
Age			0.61
<75	1562	2.01 [0.98;4.15]	
≥75	1674	2.71 [1.20;6.12]	
Duration of perm. AF			0.99
6 months to 2 years	988	2.32 [0.89;6.03]	
>2 years	2243	2.27 [1.18;4.37]	
Baseline LVEF			0.41
LVEF≤40%	680	3.45 [1.14;10.50]	
LVEF>40%	2556	1.98 [1.06;3.70]	
NYHA			0.72
No class II/III	1490	2.00 [0.81;4.97]	
Class II/III	1746	2.48 [1.26;4.86]	
CHADS			0.57
CHADS ≤2	1326	2.76 [1.16;6.57]	
CHADS >2	1908	2.02 [1.01;4.03]	
Stroke or TIA history			0.49
N	2342	2.57 [1.36;4.87]	
Y	894	1.68 [0.60;4.73]	
Coronary artery disease			0.38
N	1908	2.90 [1.35;6.22]	
Y	1327	1.77 [0.82;3.84]	
Baseline HR			0.20
HR <65 bpm	644	5.43 [1.22;24.26]	
HR ≥65 bpm	2591	1.91 [1.05;3.44]	
Baseline SBP			0.61
SBP <130 mmHg	1468	2.03 [0.95;4.33]	
SBP ≥130 mmHg	1708	2.69 [1.19;6.07]	
Digoxin			0.82
N	2166	2.15 [1.05;4.41]	
Y	1070	2.42 [1.07;5.50]	
Beta blocking agents			0.41
N	834	3.38 [1.10;10.36]	
Y	2402	2.01 [1.08;3.73]	
Vitamin K antagonist or Dabigatran			0.12
N	447	1.34 [0.51;3.48]	
Y	2789	3.10 [1.57;6.12]	
Regions			0.93
North America/Western Europe	1512	2.42 [0.85;6.86]	
Other regions	1724	2.27 [1.21;4.27]	



Adverse Events and Laboratory Abnormalities

High Level Term (preferred term)	Dronedarone N=1614	Placebo N=1609	p-value
Any Adverse Event	49.4%	37.3%	<0.001
Adverse Event; medication discontinuation	13.1%	5.0%	<0.001
Any Serious Adverse Event	7.0%	4.8%	0.008
Asthenic conditions (asthenia, fatigue)	5.5%	2.9%	<0.001
Diarrhea	6.3%	2.4%	<0.001
Gastrointestinal or abdominal pain	2.0%	0.9%	0.009
Nausea and vomiting symptoms (nausea)	4.7%	1.7%	<0.001
Breathing abnormalities (dyspnea)	4.6%	2.2%	<0.001
Edema (peripheral edema)	3.7%	1.8%	<0.001
Neurological signs and symptoms (dizziness)	4.7%	2.4%	<0.001
Rate and rhythm disorders (bradycardia)	4.2%	1.2%	<0.001
Renal failure and impairment	2.2%	0.7%	0.001
Alanine aminotransferase >3 times ULN	1.5%	0.4%	0.05

PALLAS Conclusions

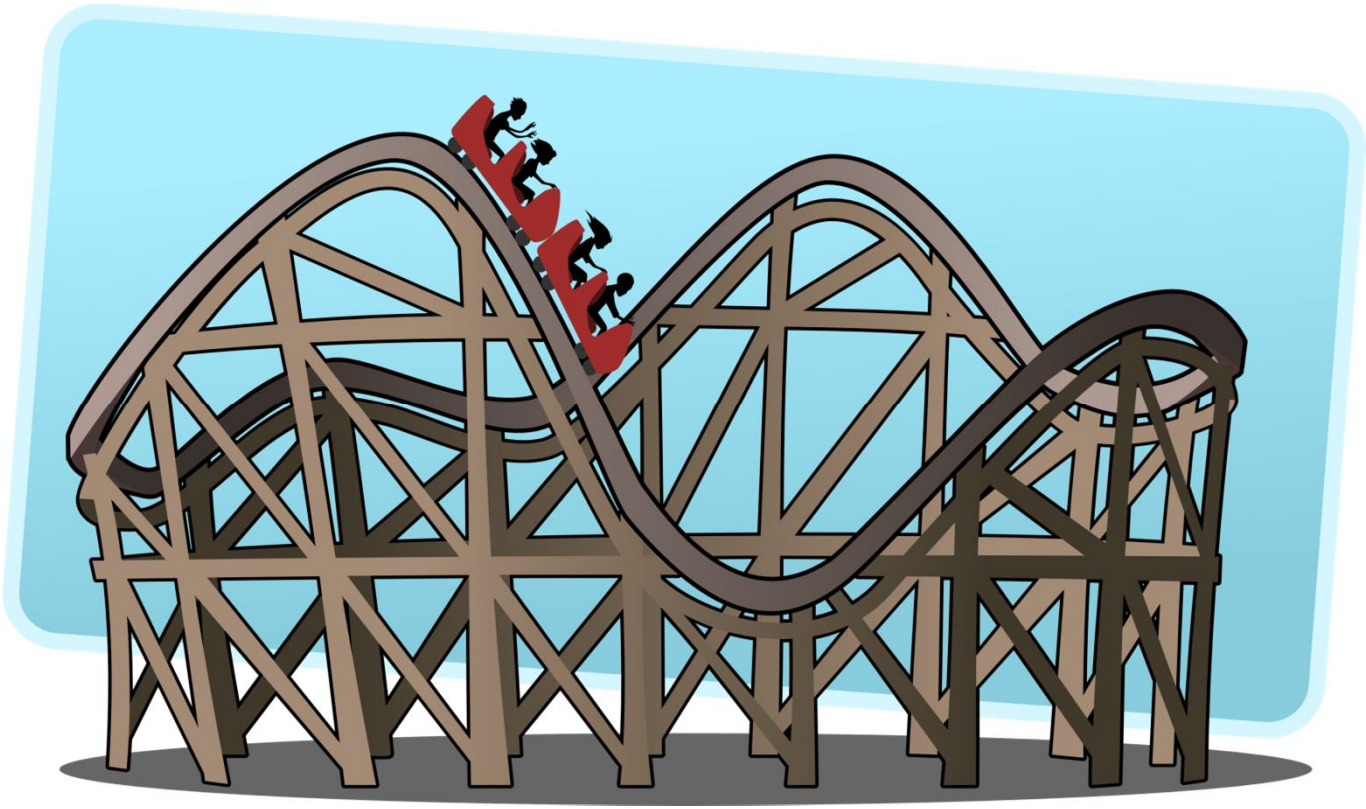
- In patients with permanent AF and major risk factors for vascular events, dronedarone increased both PALLAS primary outcomes
- This was due to increases in death, heart failure and stroke
- There was an increased rate of discontinuation of dronedarone due to adverse events
- Dronedarone should not be used in this patient population

There is no single explanation for the increase in stroke, CV death and HF observed in PALLAS

The possible hypotheses for the increase in the individual outcomes are:

- **Stroke:** The time in therapeutic range in the PALLAS trial was significantly lower on dronedarone compared to placebo, but this effect appears to be too small to explain the large increase of stroke.
- **CV death:** The increase is driven by arrhythmic death. This may be due to dronedarone-induced digoxin toxicity.
- **Heart Failure:** There is no clear explanation for the increase in HF. Permanent AF patients with greater CV risk may be more sensitive to the potential negative-inotropic effect of dronedarone.

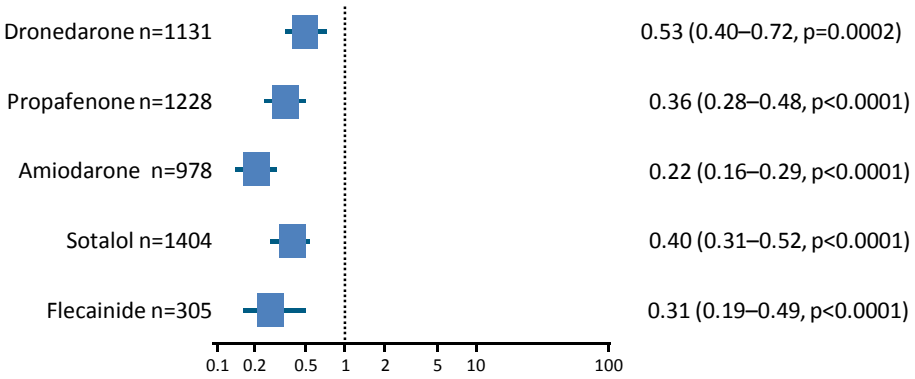
The Dronedarone Journey



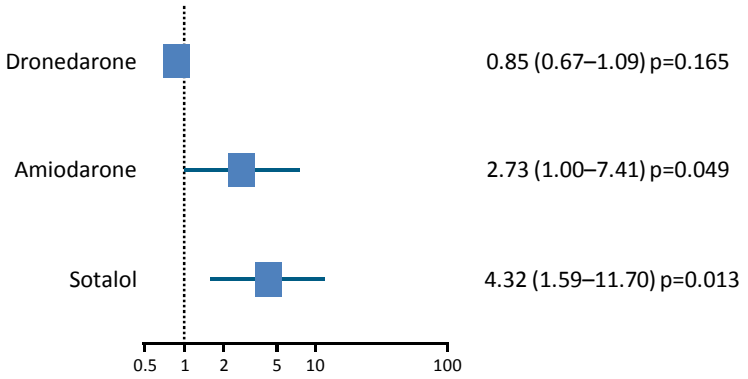
Dronedarone-Where to from here?

Antiarrhythmic drug therapy - safety and efficacy comparison based on a mixed treatment analysis*

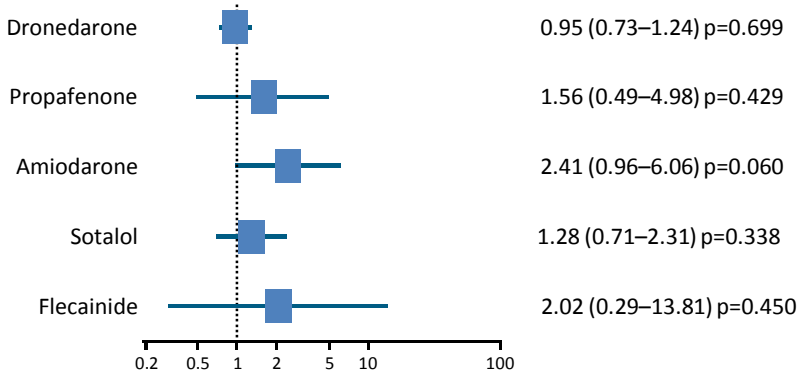
Efficacy (AF recurrence)



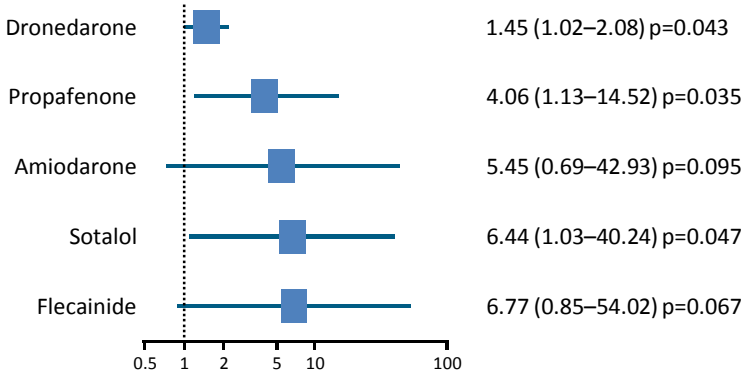
All-cause mortality



Serious adverse events



Proarrhythmic events



Data are odds ratios and 95% confidence intervals

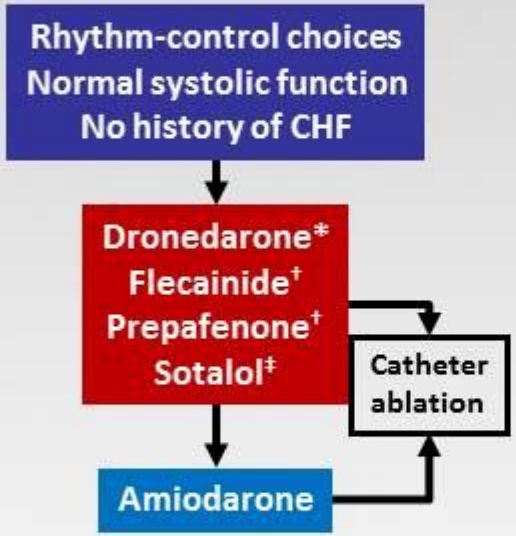
***For each individual antiarrhythmic drug versus placebo**

Freemantle N, et al. *Europace* 2011;13:329–345

For further study information including safety data, please refer to the full Multaq SmPC

Antiarrhythmic Drug Choices for Patients With No Structural Heart Disease

2011 CCS Guidelines[a]



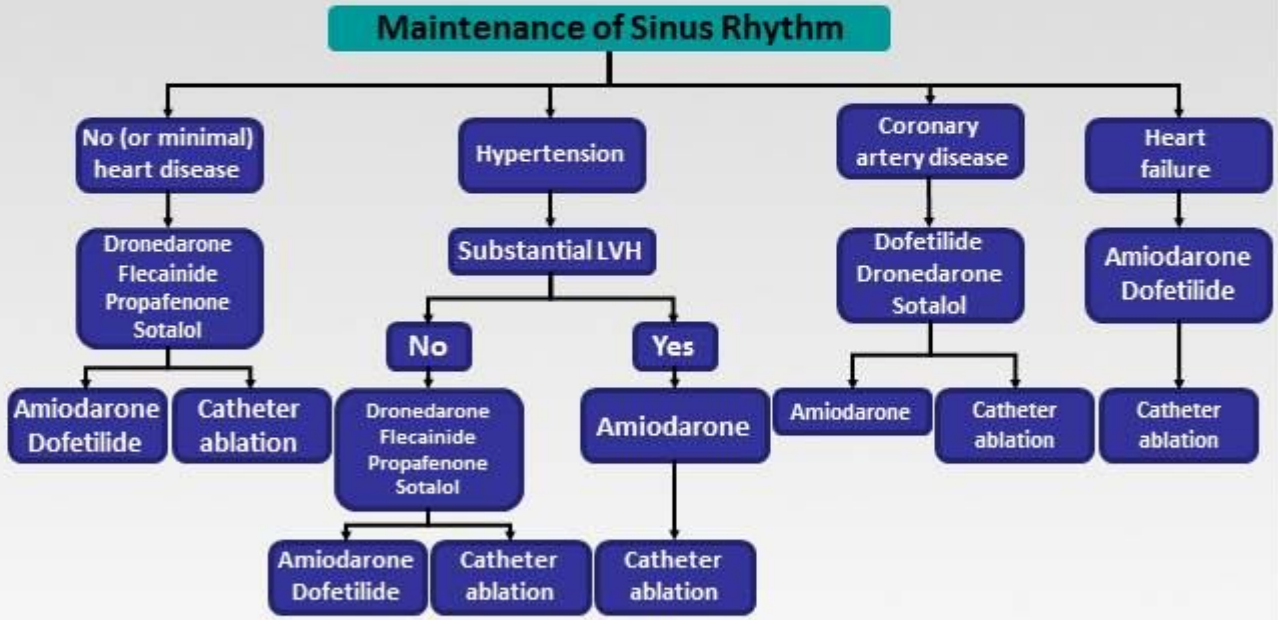
Drugs are listed in alphabetical order

*Dronedarone should be used with caution in combination with digoxin

†Class I agents should be **avoided** in CAD and should be **combined** with AV-nodal blocking agents

‡Sotalol should be used with caution in those at risk for torsades de pointes ventricular tachycardia (eg, female, age >65 y, taking diuretics)

2011 ACCF/AHA/HRS Guidelines[b]

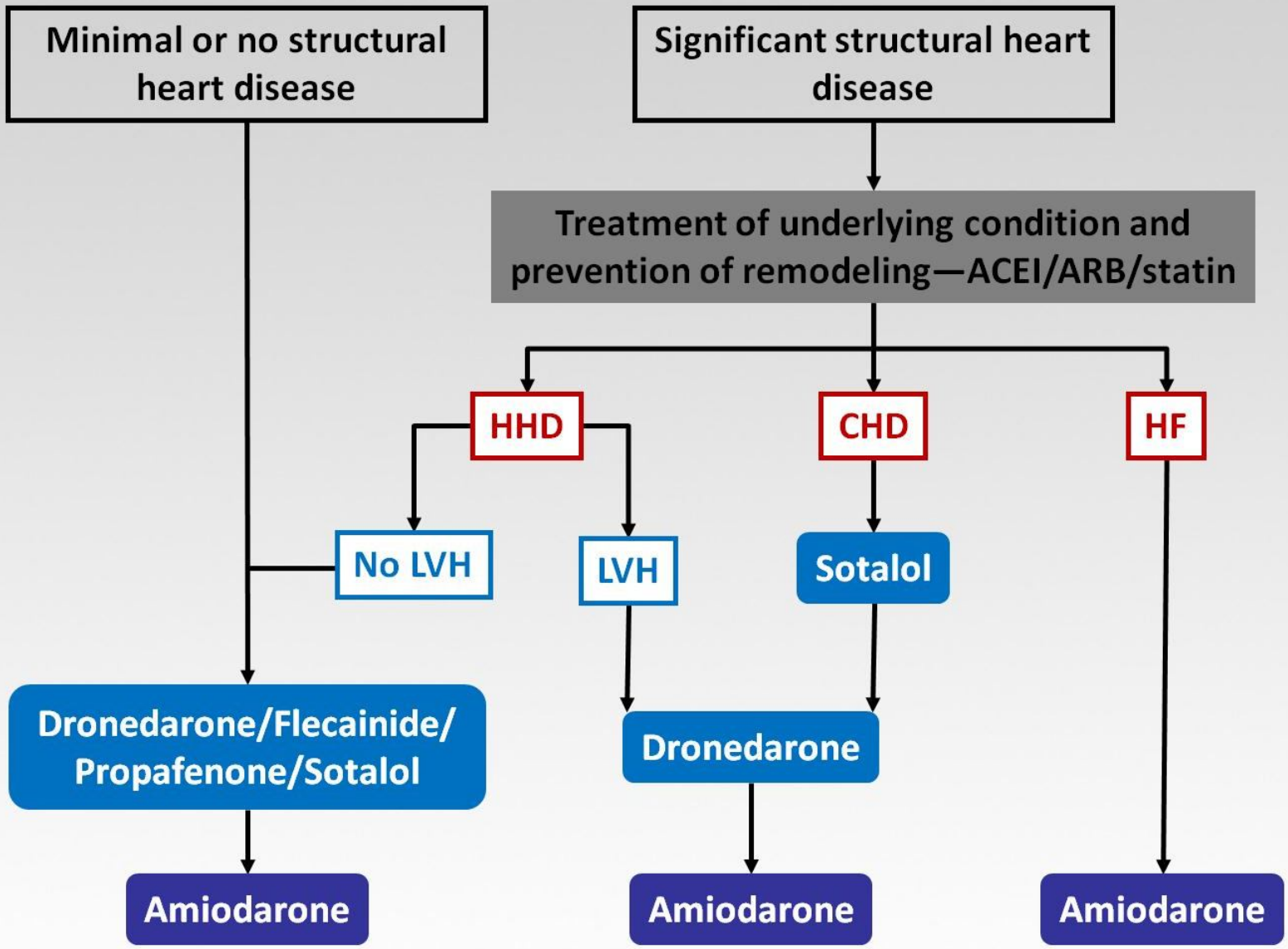


Note: Antiarrhythmic agents including dronedarone are not useful/contraindicated in atrial fibrillation that cannot be converted to normal sinus rhythm.

a. From Skanes AC, et al.[6]

b. From Wann LS, et al.[7] Republished with permission.

ESC: AF Guideline Update 2012



Camm AJ, et al.[1]

LVH

- American vs European guidelines
- Canadian guidelines
- IC and Sotalol

Toxicity

- Hepatic
- Pulmonary

Interactions

- $CYP_{450}3A4$ subtrates/inhibitors
- NOAC
- Warfarin
- QT prolonging drugs
- Digoxin
- Grapefruit juice
- CCB
- BB
- Statins

Recommendations for Dronedarone Treatment

- Discontinuation of treatment with dronedarone should be considered in the event of:
  - Recurrence of AF
  - Occurrence of adverse reactions
- Dronedarone is contraindicated in patients with the following:
  - Permanent AF
  - Unstable haemodynamic conditions
  - History of, or current heart failure or left ventricular systolic dysfunction
  - Liver and lung toxicity related to the previous use of amiodarone
- Treatment with dronedarone should be stopped during the course of treatment, in case the patient develops any of the conditions which would lead to a contraindication

Updated Indication

- Dronedarone is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF).

- Dronedarone should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure

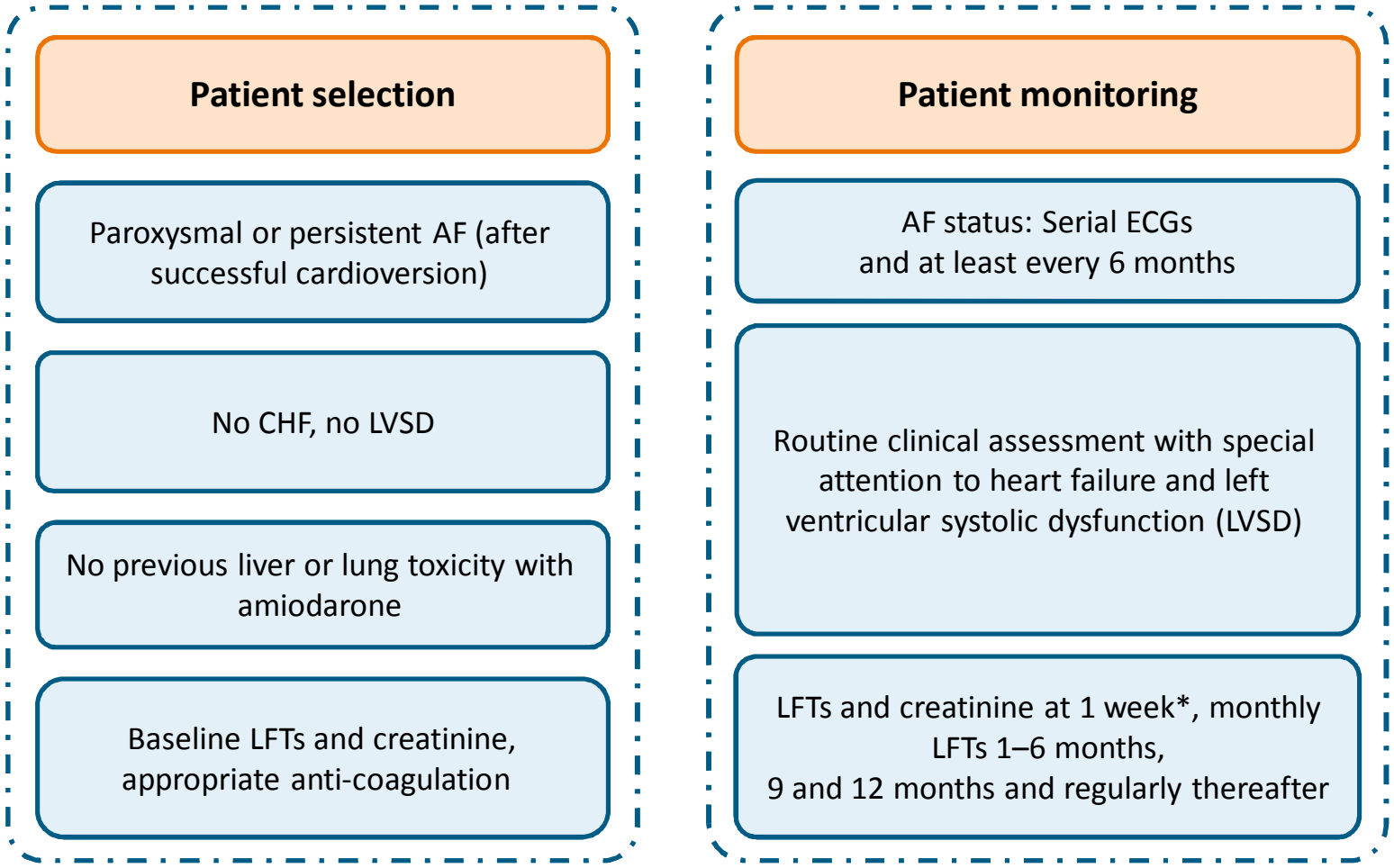
Dronedarone Prescribing Information

	Europe[a]	United States[b]
Indication	Multaq® is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent AF. Due to its safety profile (see sections 4.3 and 4.4), Multaq should only be prescribed after alternative treatment options have been considered. Multaq should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.	Multaq® indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter, with a recent episode of AF/atrial flutter and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted. Associated cardiovascular risk factors include age over 70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50 mm, or LVEF < 40%.
Contraindications*	• Permanent AF with an AF duration ≥ 6 months • Patients in unstable hemodynamic conditions • History of, or current heart failure or left ventricular systolic dysfunction • Patients with liver and lung toxicity related to the previous use of amiodarone	• Permanent AF (patients in whom normal sinus rhythm will not or cannot be restored) • Recently decompensated heart failure requiring hospitalization or class IV heart failure • Bradycardia < 50 bpm • Liver or lung toxicity related to the previous use of amiodarone

*Refer to package insert for full list of contraindications and other prescribing information.

a. Multaq.[7]
b. Multaq.[8]

Treatment with dronedarone should be initiated and monitored under specialist supervision



CHF: Congestive heart failure, LVSD: Left ventricular systolic dysfunction, LFTs: Liver function tests *At 2 weeks if there is a rise in accordance with label

Adapted from MULTAQ® SmPC Europe – September 2011. Refer to full MULTAQ® SmPC for full prescribing information.

חוזר המנהל הכללי

משרד הבריאות

הנדון: הרחבת סל שירותי הבריאות לשנת 2012

Dronedarone	Multaq	טיפול בפרפור עליות – שינוי מסגרת ההכללה בסל.

21. הוראות לשימוש בתרופה DRONEDARONE (Multaq) (130)

התרופה תינתן לטיפול במקרים האלה:

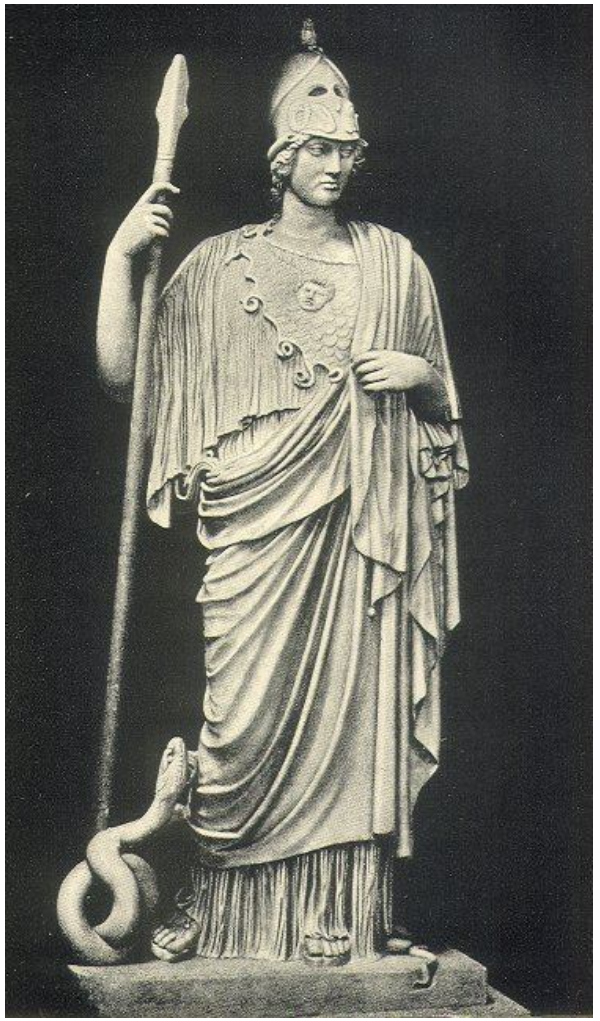
א. פרפור עליות או רפרוף עליות בחולים שפיתחו תופעות לוואי משמעותיות בטיפול ב-Amiodarone **(עדכון מסגרת ההכללה בסל)**;

ב. קו טיפול ראשון עבור חולים עם פרפור עליות התקפי ורפרוף עליות התקפי הסובלים גם ממחלת לב כלילית והם עם תפקוד טוב של חדר שמאל וללא LVH **(התוויה חדשה)**.

Greek Mythology for Cardiologists I

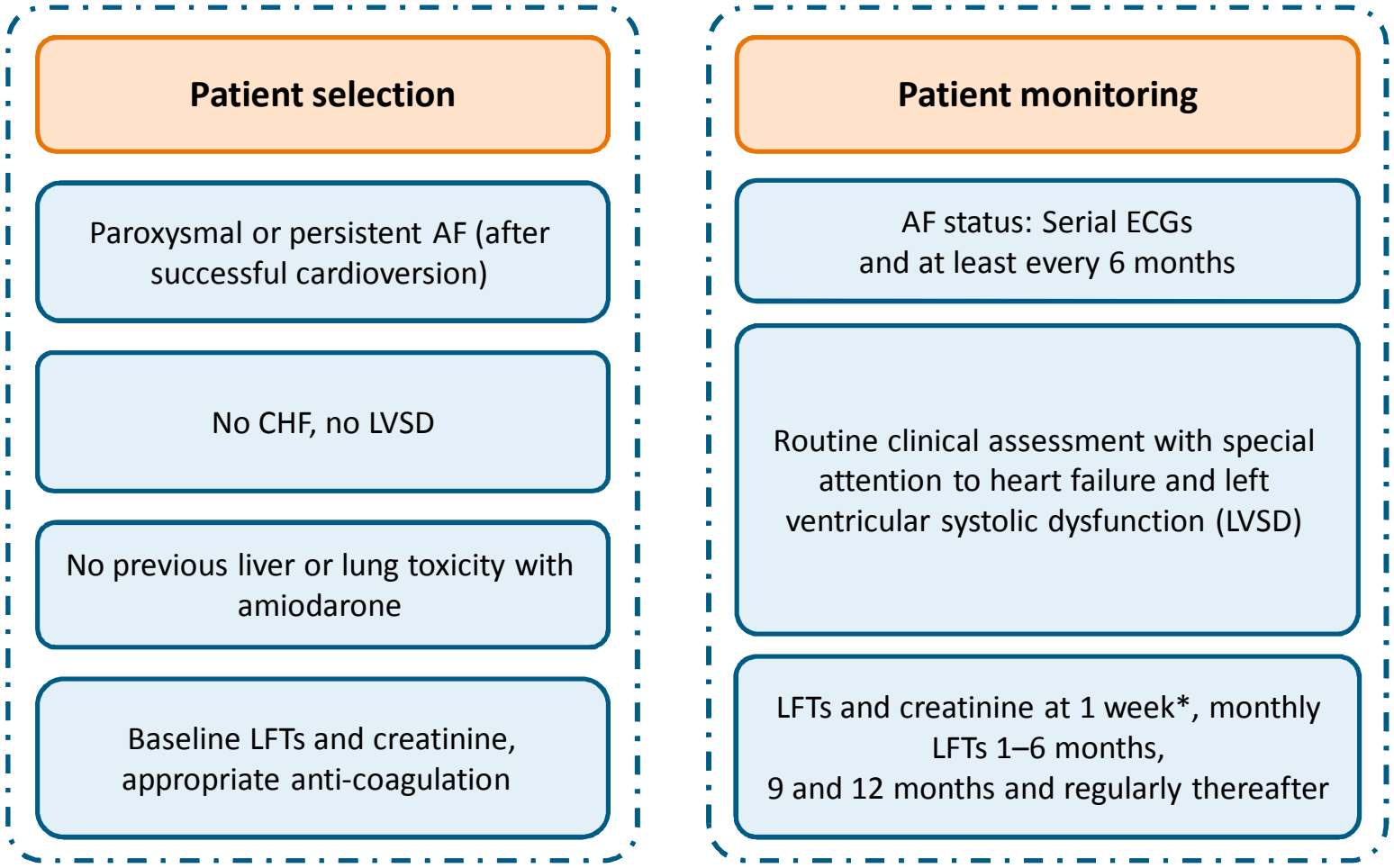
Greek Mythology for Cardiologists II

PALLAS ATHENA



Thank you

Treatment with dronedarone should be initiated and monitored under specialist supervision



CHF: Congestive heart failure, LVSD: Left ventricular systolic dysfunction, LFTs: Liver function tests *At 2 weeks if there is a rise in accordance with label

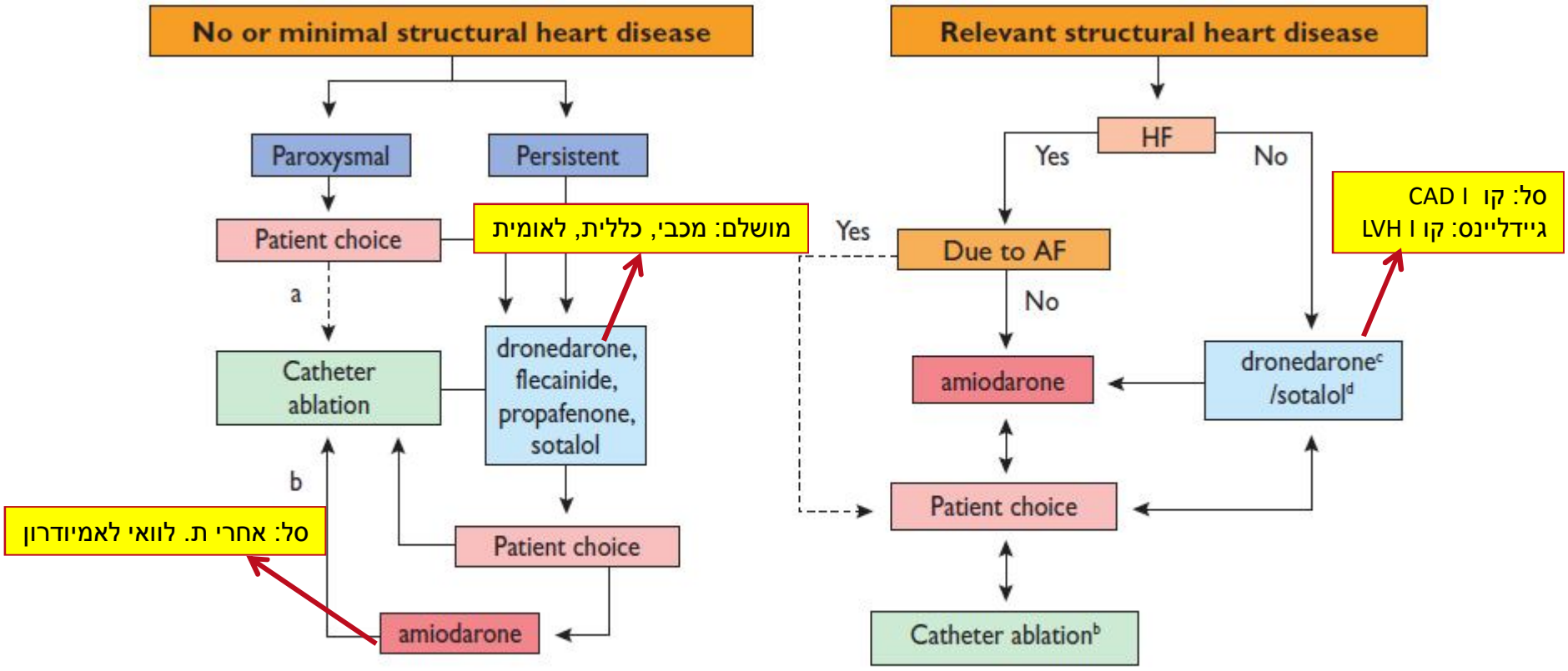
Adapted from MULTAQ® SmPC Europe – September 2011. Refer to full MULTAQ® SmPC for full prescribing information.

There are 5 key descriptors of AF patients that impact treatment choice

AF Type	Paroxysmal Persistent Permanent
Degree of symptoms	Asymptomatic Mild Moderate Severe
Co-morbid conditions	Lone AF CHF HTN, with/without LVH CHD Other CV co-morbidities
Age	<65 65-75 >75
Potential Drug-Drug-Interactions	CYP3A4 CYP2D6 P-glycoprotein substrates

Study	Patients (n)	Patient characteristics	Dose of dronedarone	Placebo controlled	Primary endpoint	Follow-up (months)	Outcome	Comments
DAFNE[152]	199	Post cardioversion	400 mg b.i.d. 600 mg b.i.d. 800 mg b.i.d.	Yes	Time to first AF recurrence	6	Dronedarone 400 mg b.i.d. significantly prolonged median time to first AF recurrence vs. placebo: 60 vs. 5.3 days ($P = 0.026$); RRR 55% (95% CI 28–72%; $P = 0.001$)	Higher doses were ineffective and were associated with discontinuation rates of 7.6% and 22.6%; conversion rates were 5.8%, 8.2%, and 14.8% vs. 3.1% on placebo
EURIDIS[153]	615	Paroxysmal or persistent AF (post cardioversion)	400 mg b.i.d.	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 41 days on dronedarone vs. 96 days on placebo ($P = 0.01$)	Ventricular rates during AF recurrence were significantly lower on dronedarone
ADONIS[153]	630	Paroxysmal or persistent AF (post cardioversion)	400 mg b.i.d.	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 59 days on dronedarone vs. 158 days on placebo ($P = 0.002$)	Dronedarone reduced ventricular rates during AF recurrence vs. placebo
ERATO[154]	630	Permanent AF with ventricular rates >80 b.p.m. on rate-controlling therapy	400 mg b.i.d.	Yes	Mean 24-h ventricular rate at 2 weeks	6	Ventricular rates were 12 b.p.m. lower on dronedarone vs. placebo	Peak heart rates during exercise were 24 b.p.m. lower on dronedarone vs. placebo
ANDROMEDA[149]	67 (1000 planned)	Congestive heart failure; EF <0.35%	400 mg b.i.d.	Yes	All-cause mortality	Median, 2	Stopped early because of increased mortality in the dronedarone arm: total mortality $n = 25$ in dronedarone group, $n = 12$ in placebo group; cardiovascular mortality $n = 24$ in dronedarone group, 9 in placebo group	
ATHENA[148]	4628	Paroxysmal or persistent AF with risk factors	400 mg b.i.d.	Yes	All-cause mortality and hospitalizations for cardiac causes	21 ± 5	Dronedarone reduced the primary endpoint vs. placebo by 24% ($P < 0.001$)	CV hospitalizations, CV mortality and hospitalizations for AF and for ACS reduced
DIONYSOS[155]	504	Persistent AF	400 mg b.i.d.	Amiodarone	AF recurrence or premature study drug discontinuation	6	Amiodarone superior to dronedarone ($P < 0.001$)	
PALLAS[5]	3236 (10 800 planned)	Permanent AF with CV risk factors	400 mg b.i.d.	Yes	1. Co-primary = composite of stroke, MI, SE, CV death 2. Co-primary = composite of first unplanned CV hospitalization or death	Median, 3.5	Stopped early because of excess events in the dronedarone group: total mortality $n = 25$ in dronedarone group, $n = 13$ in placebo group; cardiovascular mortality $n = 21$ in dronedarone group, $n = 10$ in placebo group	Only 64 of planned 844 outcome events occurred

2012 focused update of ESC Guidelines for AF Antiarrhythmic drugs and/or left atrial ablation for rhythm control of AF



AF = atrial fibrillation; HF = heart failure. [a]Usually pulmonary vein isolation is appropriate. [b]More extensive left atrial ablation may be needed. [c]Caution with coronary heart disease. [d]Not recommended with left ventricular hypertrophy. Heart failure due to AF = tachycardiomyopathy.

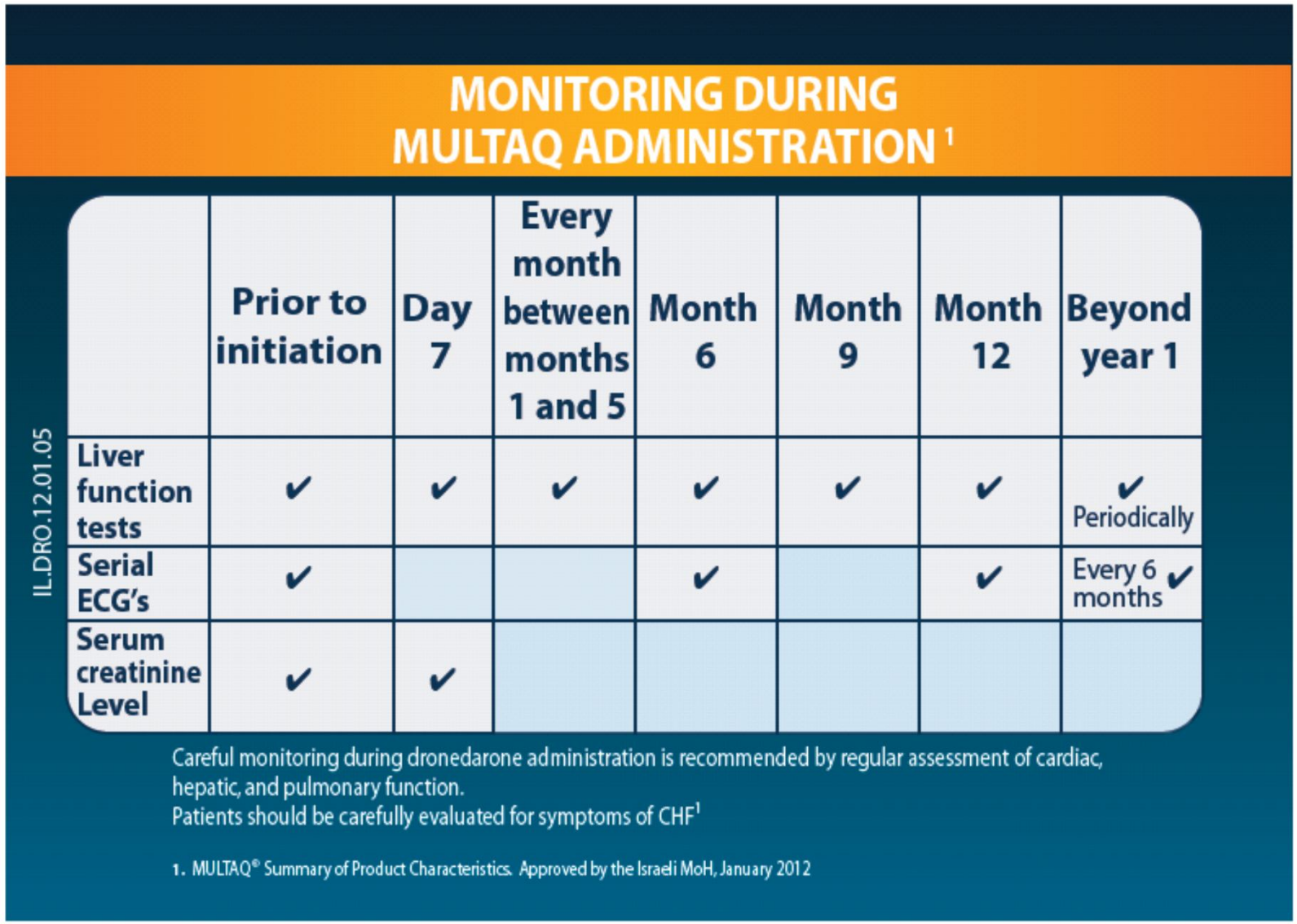
2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation * Developed with the special contribution of the European Heart Rhythm Association.Eur Heart J. 2012 Aug 24.

Meta-analysis of cardiovascular outcomes with dronedarone in patients with atrial fibrillation or heart failure.

- Dronedarone use was associated with a trend toward worse all-cause and cardiovascular mortalities and increased heart failure exacerbations

Chatterjee S et al. Am J Cardiol 2012

Monitoring



MONITORING DURING MULTAQ ADMINISTRATION [1]

	Prior to initiation	Day 7	Every month between months 1 and 5	Month 6	Month 9	Month 12	Beyond year 1
Liver function tests	✔	✔	✔	✔	✔	✔	✔ Periodically
Serial ECG's	✔			✔		✔	Every 6 months ✔
Serum creatinine Level	✔	✔					

Careful monitoring during dronedarone administration is recommended by regular assessment of cardiac, hepatic, and pulmonary function.
Patients should be carefully evaluated for symptoms of CHF[1]

1. MULTAQ® Summary of Product Characteristics. Approved by the Israeli MoH, January 2012

IL.DRO.12.01.05