



Oxford Heart Centre

Oxford Radcliffe Hospitals **NHS**  
NHS Trust

# Advances in medicines – an overview

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Honoraria received from Sanofi Aventis, MSD

# Overview

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- **‘Exciting period’ for pharmacology in arrhythmia patients**
    - Anticoagulants
    - Dronedarone
    - Vernakalant
    - Ranolazine
    - Upstream/downstream modulators
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# Dronedarone

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**New pill which treats abnormal heart rhythm could save thousands of lives every year**

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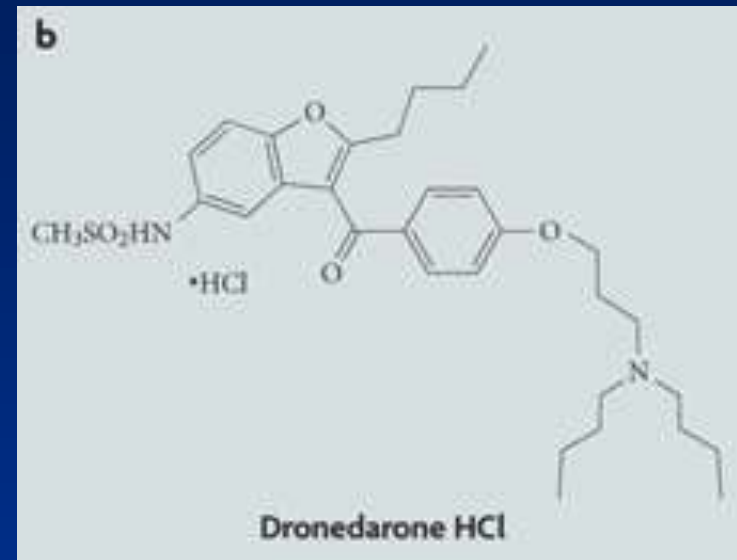
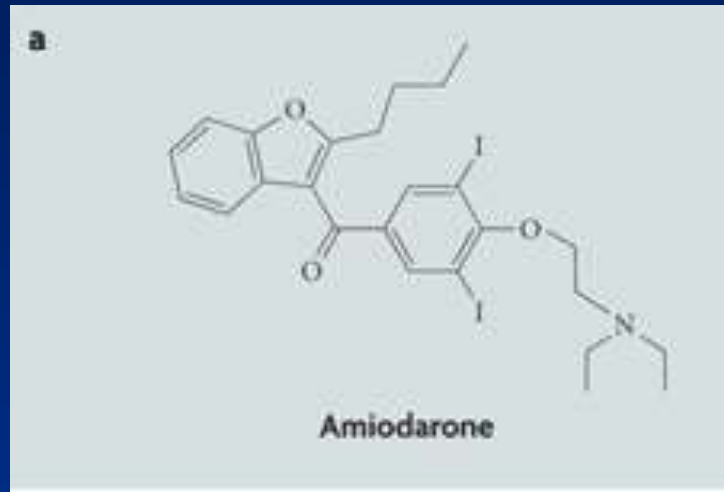
# Licensed indication

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- Adults with non-permanent AF to prevent recurrence or control rate
  - Contraindications:
    - NYHA III/IV, recent NYHA III, or LVEF<35%
    - SSS or 2/3rd degree HB
    - QTc>500msec
    - cytochrome P450 (CYP 3A4) inhibitors/inducers
    - QTc prolonging drugs
    - Severe renal or hepatic failure
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# Pharmacology

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- Class III anti-arrhythmic (similar to Amiodarone)
  - Prolongs PR, QTc, negatively inotropic/chronotropic, vasodilates and causes hypotension
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# Pharmacodynamics

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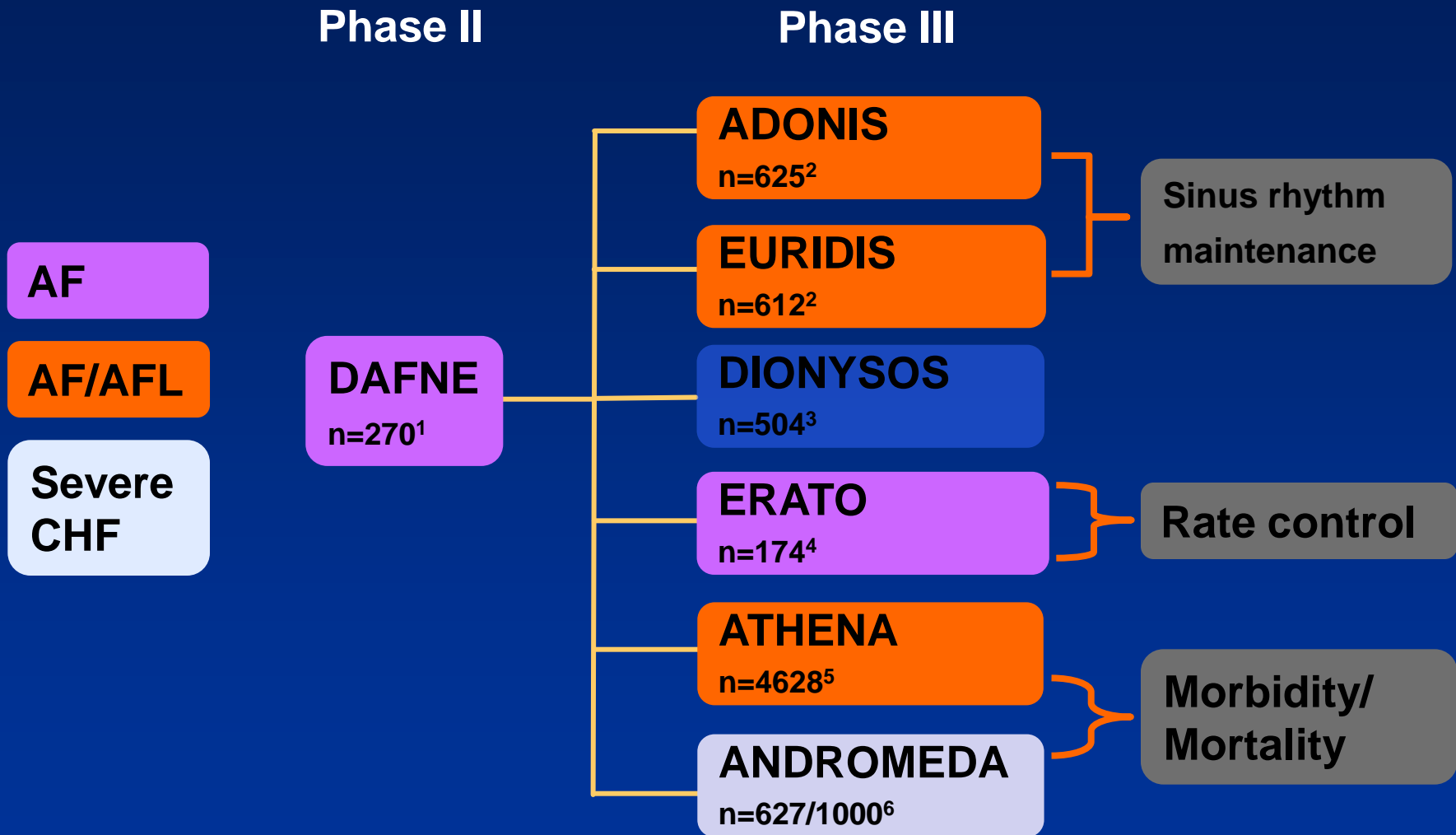
- **70% orally absorbed, 99.7% bound to plasma proteins, hepatic metabolised, renal excretion**
  - **Half life 25-30 hours**
  - **400mg bd dose with no loading regime**
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# Side effects

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- **CVS: bradycardia, Torsades de Pointes**
  - **Cutaneous: rashes, photosensitivity, pruritis**
  - **GI: dyspepsia, nausea, diarrhoea, hepatic failure**
  - **CNS: fatigue, dysgeusia**
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# Efficacy trials



# ADONIS/EURIDIS

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- RCT: Dronedarone (n=828) vs. placebo (n=409) + first line therapy, to maintain sinus rhythm (AF/AFI) over 12/12 (mean age 63yo, 69% male)
  - Trans-telephonic ECG monitoring at Day 2,3,5 and Months 3,5,7,10 or if symptoms.
  - End points:
    - 1° - time to first AF (53 v's 116 days\*),
    - 2° - symptomatic re-occurrence (37.7 v's 46.0%\*)
    - 2° - ventricular rate at re-occurrence (103 v's 117bpm\*)
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# DIONYSOS

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- RCT: Dronedarone (n=249) vs. Amiodarone (n=255), persistent AF with DC cardioversion at 2-4 weeks post randomisation. F/U over 12 months (mean age 64, 67% male)
  - 12 lead ECG at day 1, 5, 10-28, months 3, 6, 9 and 12 or if Symptoms
  - End points:
    - 1° - AF recurrence or discontinuation of drug
    - (75.5% vs. 58.8%\*),
    - 2° - safety endpoints/drug discontinuation (39.3% vs. 44.5%\*) note AF recurrence (36.5% vs. 24.3%\*)
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# ATHENA

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- RCT: Dronedarone (n=2301) vs. placebo (2327) + first line therapy for PAF or persistent AF with one risk factor over 30 months (mean age 72, 53% male)
  - End points:
    - 1° - unplanned hospitalisation or death (31.9% vs. 39.4%\*)
    - 2° - death from CV cause (2.7% vs. 3.9%\*)
    - 2° - hospitalisation due to CV events (29.35 vs. 36.9%\*)
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# ANDROMEDA

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- RCT: Dronedarone (n=627) vs. placebo (n=1000) hospitalised with CCF and severe LV systolic dysfunction (with or without AF)
  - *Stopped early (median F/U 2 months) due to excess mortality (8.1% vs. 3.8%\*)*
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# ESC guidelines

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European Heart Journal (2010) **31**, 2369–2429  
doi:10.1093/eurheartj/ehq278

**ESC GUIDELINES**

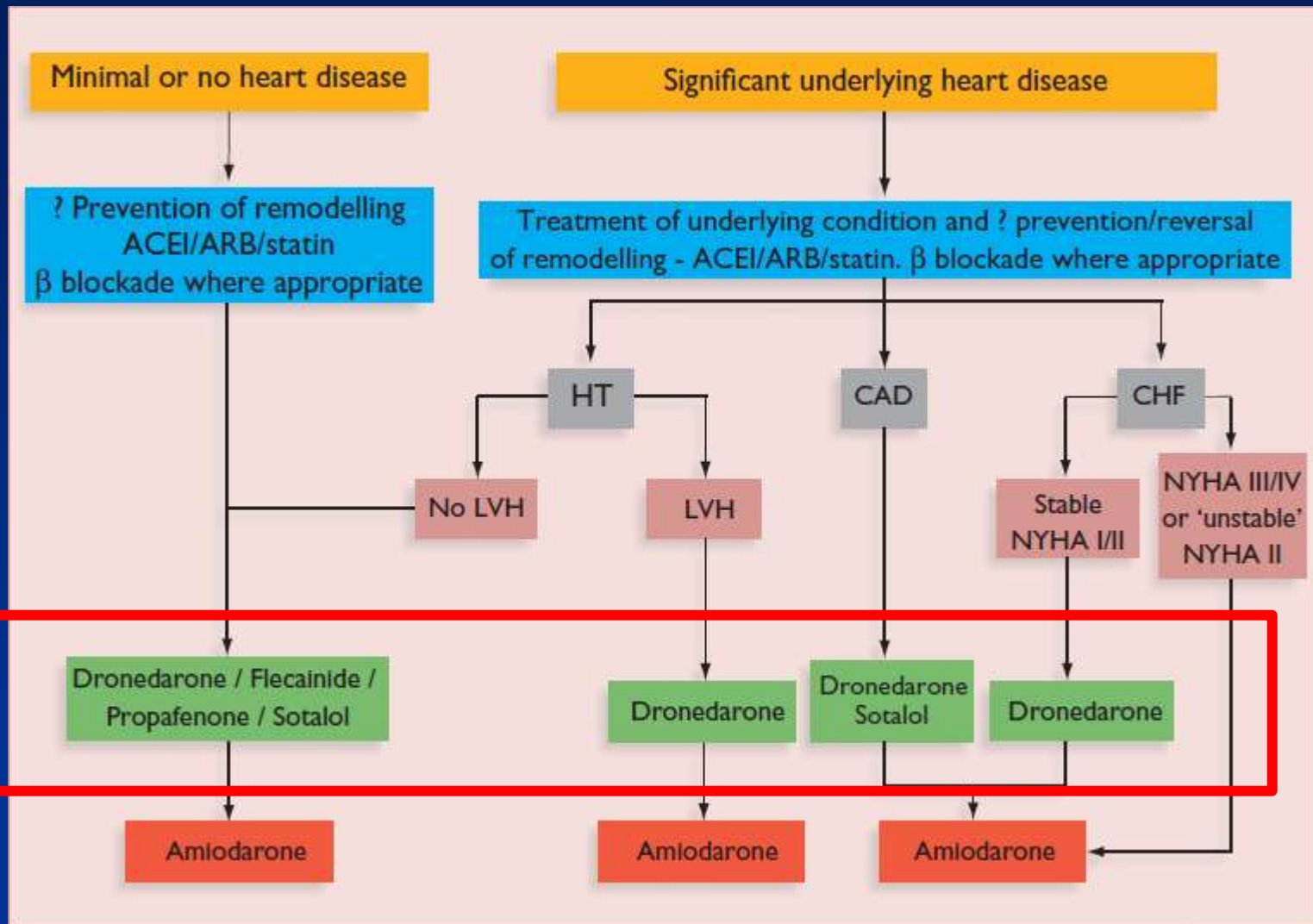
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## **Guidelines for the management of atrial fibrillation**

**The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)**

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# ESC guidelines



# NICE

- NICE TAG197
- Aug 2010

## Guidance

- 1 Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation **only** in people:
  - whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, **and**
  - who have at least one of the following cardiovascular risk factors:
    - hypertension requiring drugs of at least two different classes
    - diabetes mellitus
    - previous transient ischaemic attack, stroke or systemic embolism
    - left atrial diameter of 50 mm or greater
    - left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) **or**
    - age 70 years or older, **and**
  - who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.
- 2 People who do not meet the criteria in section 1 who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

# Post licensing issues

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- **Jan 2011: FDA warning of case reports of hepatocellular liver injury/failure and suggest monitoring of LFTs**
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# Local guidelines

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- Shared care protocol



SHARED CARE AGREEMENT

Oxfordshire

January 2011

Dronedarone ▼ (Multaq®)

For the treatment and management of non permanent atrial fibrillation

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# Local guidelines

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## **KEY PRINCIPLES FOR THE SHARED CARE PROTOCOL**

Prescribing responsibility should only be considered for transfer to primary care when a patient's clinical management and treatment is demonstrably stable.

Initiation doses of dronedarone should be prescribed by Consultant Cardiologist **ONLY**; general practitioners should only prescribe maintenance doses.

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# Local guidelines

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Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation **only** in people:

- whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, **and** who have at least one of the following cardiovascular risk factors:
  - hypertension requiring drugs of at least two different classes
  - diabetes mellitus
  - previous transient ischaemic attack, stroke or systemic embolism
  - left atrial diameter of 50 mm or greater
  - left ventricular ejection fraction less than 40%, **or**
  - age 70 years or older, **and** who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.

# Local guidelines

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- **Baseline renal and liver function**
  - **7-10 days renal/LFT**
  - **Serum creatinine ↑**
  - **3 and 9 month review**
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# Local guidelines

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- Monthly LFTs for 6 months
- LFTs 9 and 12 months

If alanine transaminase (ALT) levels are elevated to  $\geq 3 \times$  upper limit of normal (ULN), levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be  $\geq 3 \times$  ULN after re-measurement, dronedarone treatment should be withdrawn.

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# Audit

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National Institute for  
Health and Clinical Excellence

Dronedarone for the treatment of  
non-permanent atrial fibrillation

**Audit support**

Implementing NICE guidance

# Audit

## Patient data collection tool for 'Dronedarone for the treatment of non-permanent atrial fibrillation'

Complete one form for each patient or episode.

Patient identifier:	Sex:	Age:	Ethnicity:
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No.	Date item no.	Criteria	Yes	No	NA/ Exceptions*
1		If the patient is receiving dronedarone:			
	1.1	• Is this as a second-line treatment option (that is, when atrial fibrillation is not controlled by first-line therapy, usually including beta-blockers)?	<input type="checkbox"/>	<input type="checkbox"/>	
	1.2	• Do they have at least one of the following cardiovascular risk factors?	<input type="checkbox"/>	<input type="checkbox"/>	
		– Hypertension requiring drugs of at least two different classes,			
	1.3	– Diabetes mellitus.	<input type="checkbox"/>	<input type="checkbox"/>	
	1.4	– Previous transient ischaemic attack, stroke or systemic embolism.	<input type="checkbox"/>	<input type="checkbox"/>	A
	1.5	– Left atrial diameter of 50 mm or greater.	<input type="checkbox"/>	<input type="checkbox"/>	
	1.6	– Left ventricular ejection fraction less than 40%.	<input type="checkbox"/>	<input type="checkbox"/>	
	1.7	– Age 70 years or older.	<input type="checkbox"/>	<input type="checkbox"/>	
	1.8	• Do they have unstable New York Heart Association (NYHA) class III or IV heart failure?	<input type="checkbox"/>	<input type="checkbox"/>	

\*Circle exception codes as appropriate. Details of exceptions are listed at the end of the patient data collection tool.



### Exception code

A – People who do not meet the criteria in 1.1(above) who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

# PALLAS

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- RCT: Dronedarone vs. placebo in permanent AF
  - *Stopped early - 2.3 fold increase in CV events (stroke, systemic emboli, MI, CV death) and 1.5 fold increase in hospitalisation and all cause mortality in dronedarone arm*
  - EMA recommendation recently
-

# ESC guidelines – acute medical treatment

Drug	Dose	Follow-up dose	Risks
Amiodarone	5 mg/kg i.v. over 1 h	50 mg/h	Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecainide	2 mg/kg i.v. over 10 min, or 200–300 mg p.o.	N/A	Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Ibutilide	1 mg i.v. over 10 min	1 mg i.v. over 10 min after waiting for 10 min	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.
Propafenone	2 mg/kg i.v. over 10 min, or 450–600 mg p.o.		Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg i.v. over 10 min after 15 min rest	So far only evaluated in clinical trials; recently approved. <sup>68–70a</sup>

# **AVRO** (Active Controlled, Multicenter Study of Vernakalant Injection Versus Amiodarone in Subjects with Recent Onset Atrial Fibrillation)

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- Novel IV agent for acute conversion of AF
- Blocks early-activating K<sup>+</sup> channels and frequency-dependent Na<sup>+</sup> channels
- Arrhythmia Conversion Trial I (ACT I) trial, successfully converted more patients to normal sinus rhythm than placebo.
- Randomized, double-blind, multicenter superiority trial
- 254 patients with AF
- 116 patients in each group receiving at least one dose of the study drug
- 30% of patients in both treatment arms had no AF episodes prior to the initial diagnosis; one-third had three or more episodes

# AVRO

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- Vernakalant - 10-minute infusion of 3 mg/kg followed by an additional 10-minute infusion of 2 mg/kg if needed after a 15-minute observation period
- Amiodarone - 60-minute infusion of 5 mg/kg followed by an additional 60-minute maintenance infusion of 50 mg
- Patients in sinus rhythm at 90 minutes: 51.7% vs. 5.2% ( $p < 0.0001$ )
- No torsades de pointes, VF, sustained VT or drug-related deaths
- Side effects primarily nausea, a distorted sense of taste, cough, and sneezing.

# Ranolazine

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- Late sodium current inhibitor
  - Treatment for chronic angina
  - Observation of reduction in arrhythmias in acute ischaemia
  - Also Long QT
  - AF
  - Clinical trials
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# Ranolazine

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- MERLIN TIMI 36

	Ranolazine (%)	Placebo (%)	p Value
Polymorphic VT $\geq$ 8 beats	1.2	1.4	0.40
Sustained VT ( $\geq$ 30s)	0.44	0.44	0.98
Monomorphic VT	0.13	0.22	0.37
Polymorphic VT	0.32	0.22	0.46

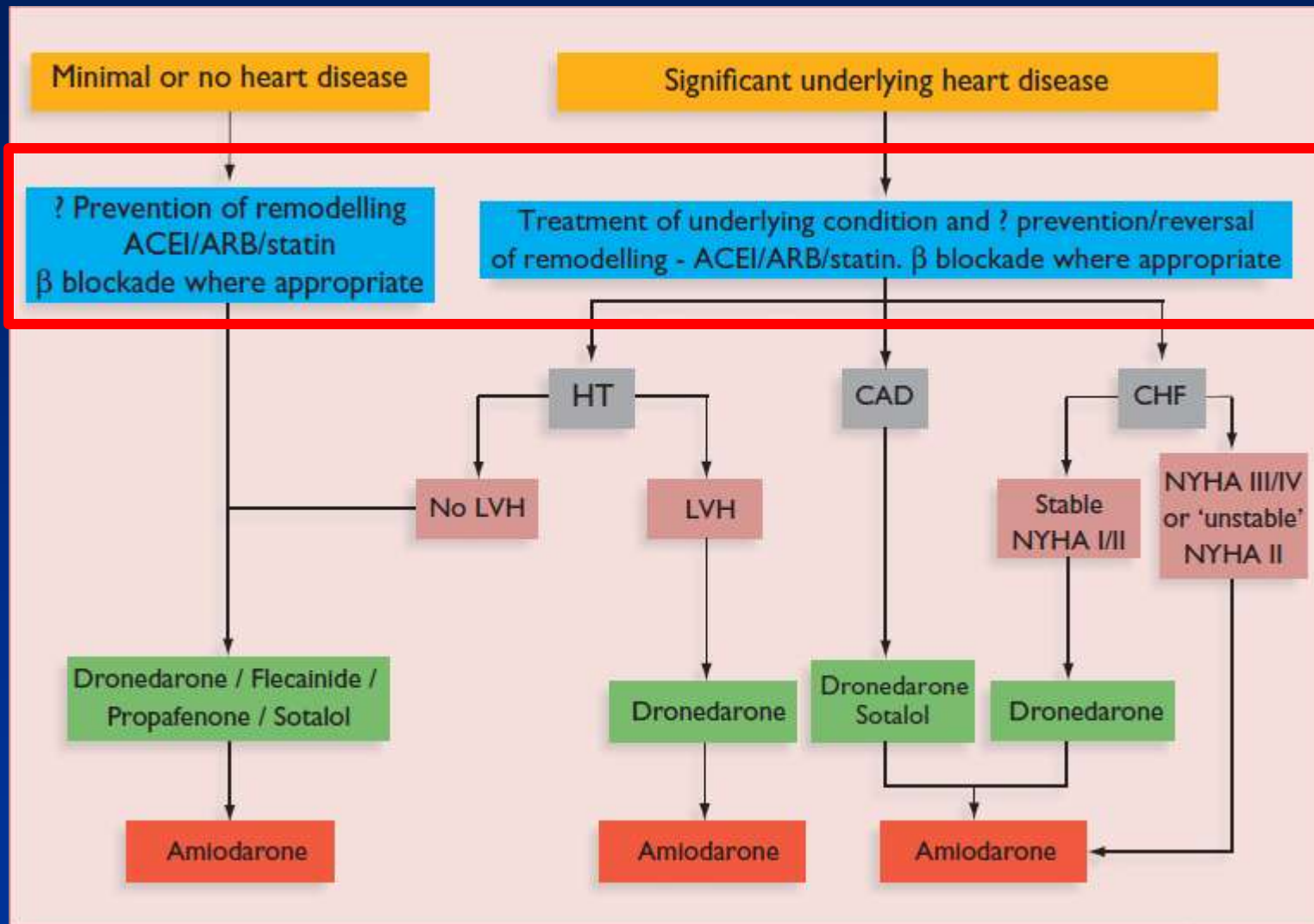
- Also reduced SVTs
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# Ranolazine

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- Small studies suggest safe in structural heart disease
  - May work as pill in the pocket
  - No randomised studies of AA effect reported yet
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# ESC guidelines



# ACEI/ARB

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- RAAS inhibition ↓ fibrosis in experimental models
  - +ve effect in select populations with AF  
e.g. LV dysfunction
  - GISSI-AF/ANTIPAF/ACTIVE-I : not favorable
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# Statins

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- Primary prevention – maybe in post op AF
  - Secondary prevention – trials ongoing
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# PUFA

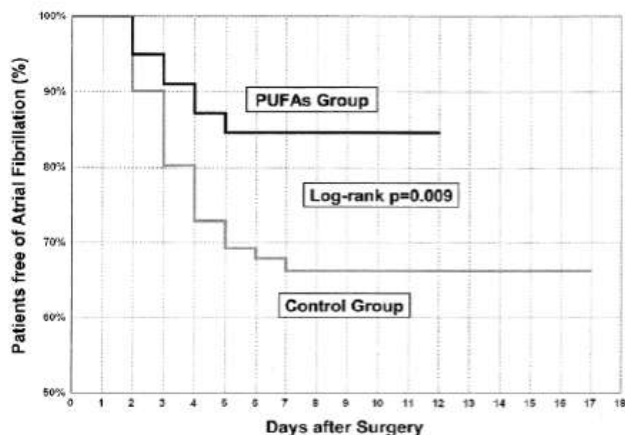
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 doi:10.1016/j.jacc.2008.02.079

## N-3 Fatty Acids for the Prevention of Atrial Fibrillation After Coronary Artery Bypass Surgery A Randomized, Controlled Trial

Leonardo Calò, MD, FESC, Leopoldo Bianconi, MD, Furio Colivicchi, MD, FESC, Filippo Lamberti, MD, Maria Luisa Loticchio, MD, Ermenegildo de Ruvo, MD, Antonella Meo, MD, Claudio Pandolfi, MD, FESC, Mario Stahano, MD, Massimo Santini, MD, FESC, FACC

Rome, Italy



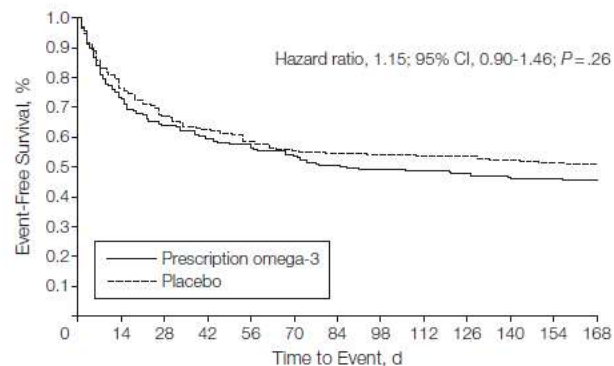
## Efficacy and Safety of Prescription Omega-3 Fatty Acids for the Prevention of Recurrent Symptomatic Atrial Fibrillation A Randomized Controlled Trial

Peter B. Kowey, MD  
 James A. Reiffel, MD  
 Kenneth A. Ellenbogen, MD  
 Gerald V. Naccarelli, MD  
 Craig M. Pratt, MD

**Context** Atrial fibrillation (AF) is common, yet there remains an unmet medical need for additional treatment options. Current pharmacological treatments have limited efficacy and significant adverse events. Limited data from small trials suggest omega-3 polyunsaturated fatty acids may provide a safe, effective treatment option for AF patients.

**Objective** To evaluate the safety and efficacy of prescription omega-3 fatty acids (prescription omega-3) for the prevention of recurrent symptomatic AF.

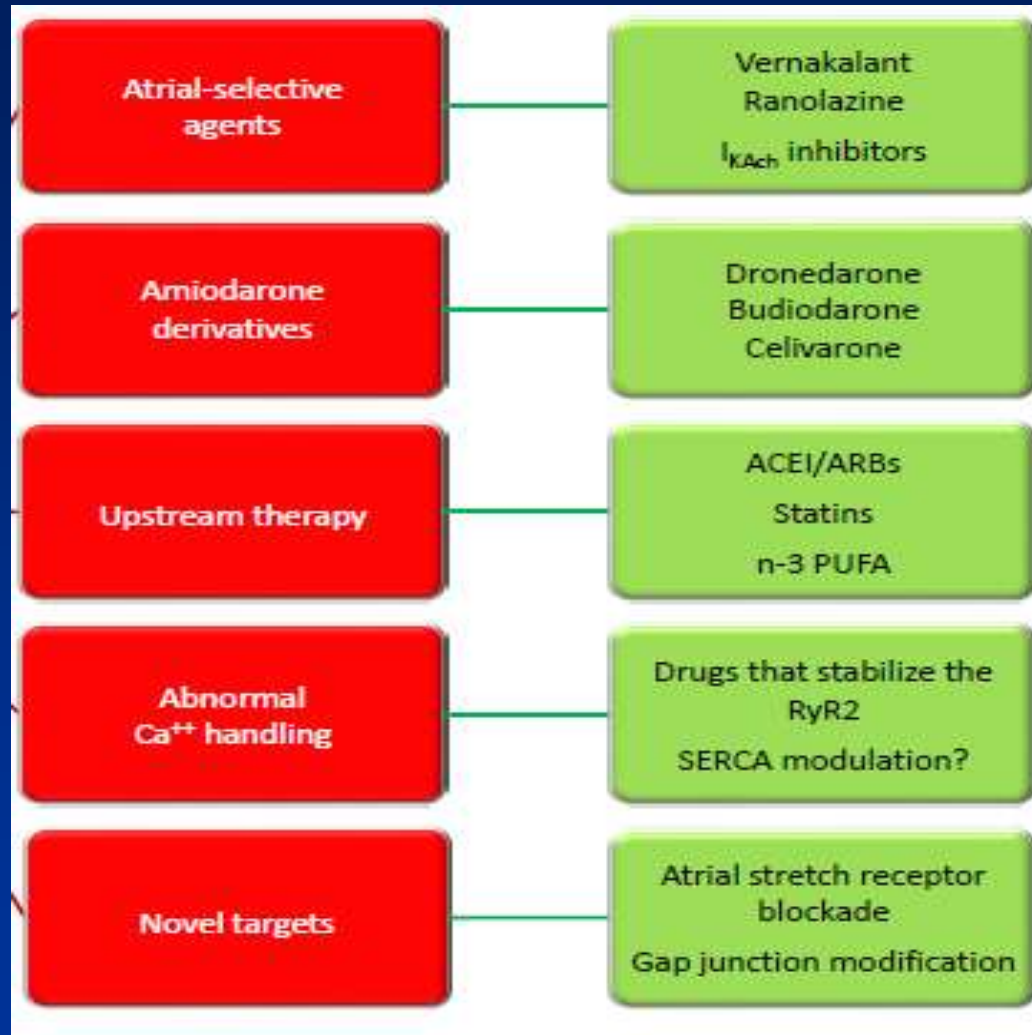
**Figure 2.** First Recurrence of Symptomatic Atrial Fibrillation for the Paroxysmal Stratum



No. of participants at risk	
Prescription omega-3	258 184 158 144 137 128 119 114 113 109 104 102 81
Placebo	269 205 175 159 148 141 136 133 131 130 128 124 97

Analysis is based on a Cox proportional hazards model adjusting for treatment, region, and use of angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and statin.

# Summary



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*Any Questions*

