

# Updates in Antiarrhythmic Pharmacotherapy

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## Objectives

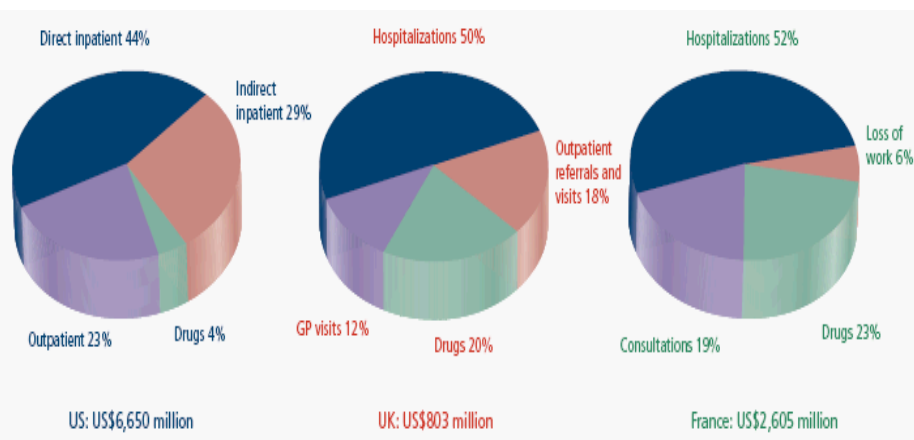
- Describe the pharmacologic activity of dronedarone
- Outline key findings in the clinical trials of dronedarone
- Identify potential places in therapy for use of dronedarone

# Atrial fibrillation

- 2.3 million Americans have AF<sup>1</sup>
- 2.5-fold increase expected in the next 40 years<sup>1</sup>
- 3 major classifications<sup>2</sup>:
  - Paroxysmal
  - Persistent
  - Permanent
- 8 – 9% progress from paroxysmal to permanent<sup>3</sup>
- 25% of progress to permanent within 60 months<sup>3</sup>

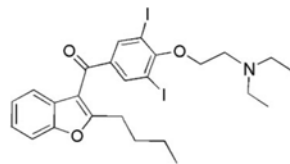
1. Go A, Hylek E, Phillips K, et al. ATRIA Study: JAMA 2001;285(18):2370-5.
2. Fuster V, Ryden LE, Cannon DS, et al. ACC/AHA/ESC 2006 guidelines for management of AF. Circulation 2006;114:700-752.
3. CARAF study: Kerr CR, Humphries KH, Talajic M et al. Am Heart J 2005;149: 486-96.

# Associated Costs

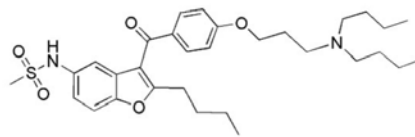


Coyne KS, Paramore C, Grandy S et al. Value Health, 2006;9:348-56.

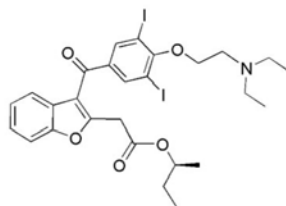
## Amiodarone and Related Compounds



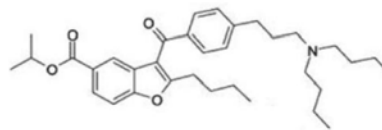
**Amiodarone**



**Dronedarone**



**Budiodarone**



**Celivarone**

Mason, PK and DiMarco JP. Circ Arrhythm Electrophysiol 2009;2:588-97.

## Pharmacology

- Multichannel blocker with many effects:
  - Delayed rectifier current ( $I_{Kr}$  and  $I_{Ks}$ )
  - L-type calcium currents ( $I_{Ca-L}$ )
  - Inward sodium current ( $I_{Na}$ )
  - Inward rectifier potassium current ( $I_{K1}$ )
  - Noncompetitive  $\alpha$ - and  $\beta$ -adrenergic antagonist
  - Inhibits pacemaker current ( $I_f$ )
  - Inhibits potassium current ( $I_{KAch}$ )

Mason, PK and DiMarco JP. Circ Arrhythm Electrophysiol 2009;2:588-97.

## Pharmacokinetics

- Well-absorbed
- Undergoes extensive first-pass metabolism via 3A4
- Elimination half-life 13-24 hours
- N-debutyl derivative is less potent, but active
- Trough plasma concentrations are 60 – 150 ng/mL
- Avoid in severe hepatic insufficiency

## Clinical Trials

## Major Clinical Trials

| Trial             | Patients | Comparator | Duration  |
|-------------------|----------|------------|-----------|
| EURIDIS<br>ADONIS | 1237     | Placebo    | 12 months |
| ERATO             | 630      | Placebo    | 14 days   |
| ANDROMEDA         | 617      | Placebo    | 7 months  |
| ATHENA            | 4628     | Placebo    | 21 months |
| DIONYSOS          | 504      | Amiodarone | 7 months  |

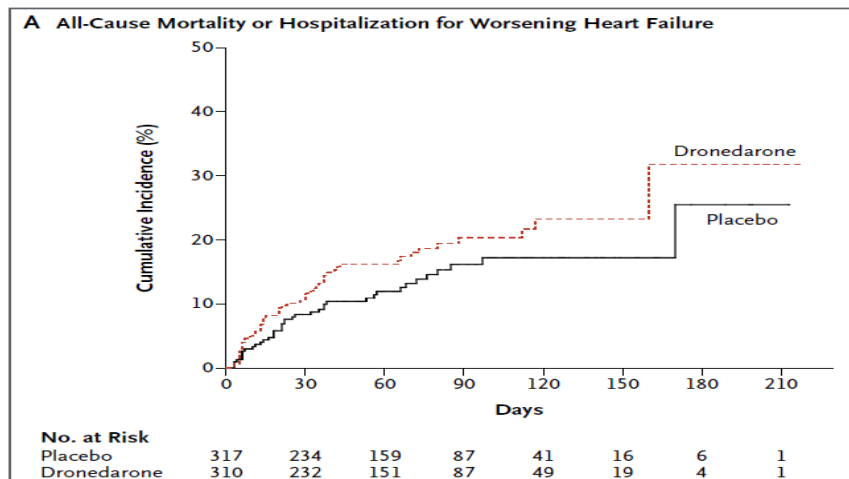
## ATHENA

**Table 3: Incidence of Endpoint Events**

|   | Placebo<br>(N= 2327) | MULTAQ<br>400mg BID<br>(N= 2301) | HR   | 95%<br>CI     | p-Value |
|---|----------------------|----------------------------------|------|---------------|---------|
| <b>Primary endpoint</b>   |                      |                                  |      |               |         |
| Cardiovascular hospitalization or death from any cause                            | 913 (39.2%)          | 727 (31.6%)                      | 0.76 | [0.68 - 0.83] | <0.0001 |
| <b>Components of the endpoint (as first event)</b>                                |                      |                                  |      |               |         |
| • Cardiovascular hospitalization  | 856 (36.8%)          | 669 (29.1%)                      |      |               |         |
| • Death from any cause  | 57 (2.4%)            | 58 (2.5%)                        |      |               |         |
| <b>Secondary endpoints (any time in study)</b>                                    |                      |                                  |      |               |         |
| Death from any cause  | 135 (5.8%)           | 115 (5.0%)                       | 0.86 | [0.67 - 1.11] | 0.24    |
| Cardiovascular hospitalization  | 856 (36.8%)          | 669 (29.1%)                      | 0.74 | [0.67 - 0.82] | <0.0001 |
| <b>Components of the cardiovascular hospitalization endpoint (as first event)</b> |                      |                                  |      |               |         |
| • AF and other supraventricular rhythm disorders                                  | 456 (19.6%)          | 292 (12.7%)                      | 0.61 | [0.53 - 0.71] | <0.0001 |
| • Other   | 400 (17.2%)          | 377 (16.4%)                      | 0.89 | [0.77 - 1.03] | 0.11    |

Hohnloser S, Crijns J, Eickels M, et al. N Engl J Med 2009; 360:668-78.

# ANDROMEDA



Kober L, Torp-Pedersen C, McMurray J, et al. N Eng J of Med 2008;358:2678-87.

# ANDROMEDA

- Stopped after 7 months average follow-up by DSMB (2 month data yielded 25D v. 12P deaths)
- Outcome driven by worsened HF
- Resultant black-box warning
- Use now limited/contraindicated in EF less than 35%

## Place in therapy

- Questions still remain regarding the cost and efficacy of this medication in the AF/AFL treatment algorithm

## FDA Approval Language

- To reduce risk of CV hospitalization in AF/AFL
- With a recent episode of AF/AFL and CV risk factors who are in NSR or will be cardioverted
  - Aged greater than 70 years
  - Hypertension
  - DM
  - Prior CVA
  - Left atrial diameter equal to or greater than 50 mm
  - LVEF less than 40%

Multaq Prescribing Info. <http://products.sanofiaventis.us/multaq/multaq.html>  
Accessed 08/28/2010.

## National Institute for Health and Clinical Excellence (UK) Recommendations 7/31/2010

- Dronedarone is recommended as an option **only** in people with:
  - Atrial fibrillation not controlled by beta-blockers **and**
  - One of the following cardiovascular risk factors:
    - HTN requiring drugs of at least two different classes
    - diabetes mellitus
    - previous TIA, stroke or systemic embolism
    - left atrial diameter of 50 mm or greater
    - LVEF less than 40% (noting that use with LVEF < 35% is not recommended)
    - age 70 years or older
  - AND who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.

<http://www.nice.org.uk/nicemedia/live/11750/49792/49792.pdf> Accessed 8/28/10.