Emerging Pharmacologic Therapy of Atrial Fibrillation: 2009

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During the course of my career I have been a consultant or advisor to, investigator for, or on the speaker's bureau of:

Abbott Laboratories, Astellas Pharma, AstraZeneca Pharmaceuticals, Berlex, BI, Boston Scientific, Bristol-Myers Squibb, Cardiome, Ciba-Geigy, Cordis, CPI, CV Therapeutics, GlaxoSmithKline Pharmaceuticals, Guidant, Instromedics, Knoll, Lifewatch, Medtronic, Merck, Novartis, Parke-Davis, Pfizer, P&G, Reliant, Roche, Sanofi-Aventis, Searle, Solvay, Survival Tech, Telectronics, 3M, Wyeth-Ayerst, Xention Discovery

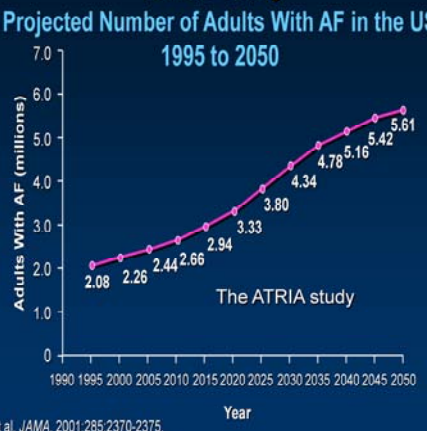
I have no investments in medical industry companies.

My presentation has been designed to be free of any actual conflict of interest as regards the above relationships.

Dept. of Medicine, Division of Cardiology, Section of Electrophysiology, CUMC

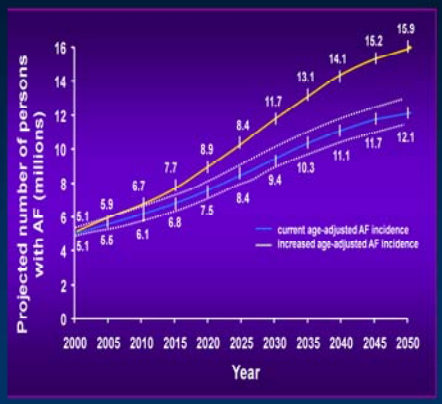
Atrial Fibrillation is the Most Common Symptomatic Tachyarrhythmia Physicians Encounter. And, it is Growing!

Future of Atrial Fibrillation
ATRIA Study

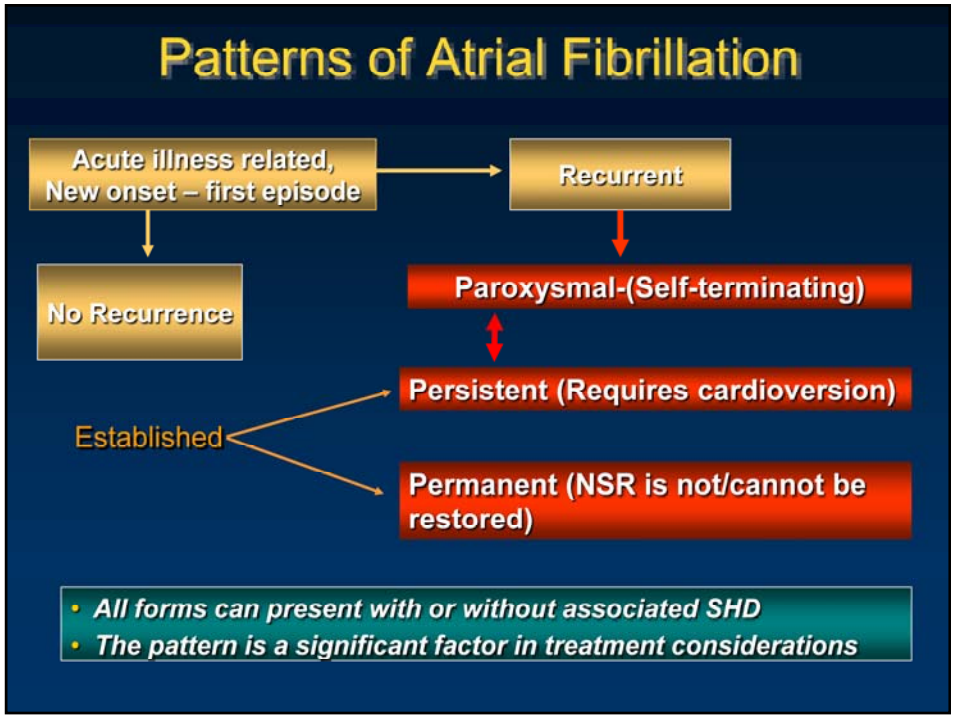


Go et al. *JAMA*. 2001;285;2370-2375.

2006 Revised Projected Number of Individuals with AF



Miyasaka Y, et al. *Circulation*. 2006;114:119-125.



Atrial fibrillation (AFib) can be generally divided into 3 groups: paroxysmal, persistent, and permanent

Patients with paroxysmal AFib (PAF) go in and out of AFib for variable periods of time, and AFib terminates to normal sinus rhythm (NSR) spontaneously without specific interventions

Patients with persistent AFib do not go back into sinus rhythm without pharmacologic or electrical cardioversion. Patients with persistent AFib will maintain sinus rhythm for variable periods of time following conversion to sinus rhythm

Patients may shift between persistent and paroxysmal AFib

In permanent AFib, the patient cannot be returned to sinus rhythm using pharmacologic or electrical modalities. If sinus rhythm is achieved, the patient will only maintain it for a very brief time and, thus, AFib is essentially permanent

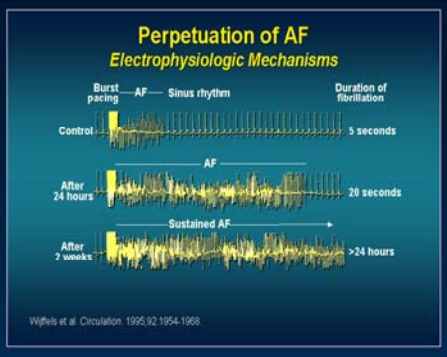
Therapeutic Interventions in AF

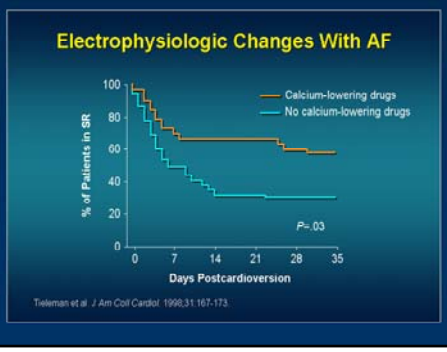
- In any disorder, the goals of therapy are to make the patient feel better, and, if possible, to live longer, while minimizing any adverse consequences from the therapy itself.
- In patients with atrial fibrillation, these therapeutic goals may be pursued with:
  - Rate control *
  - Rhythm control *
  - Prevention of emboli *
  - Therapies modifying associated SHD ("upstream therapies")

* Pharmacologic and non-pharmacologic

Electrical Remodeling

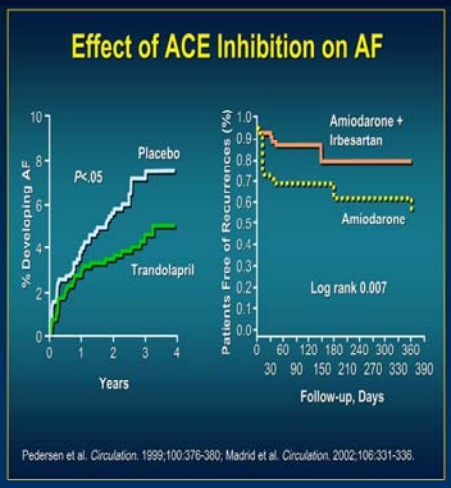
- Electrical remodeling results shortening of refractory periods, metabolic alterations, and secondary geometric, fibrotic, and mechanical alterations that lead to larger atrial with short RP's. This condition can sustain more reentrant wavelets.
- Atrial fib begets atrial fib.
- May be, at least initially, a Ca^{++} overload process and prevented or reduced with CCB's (verapamil).

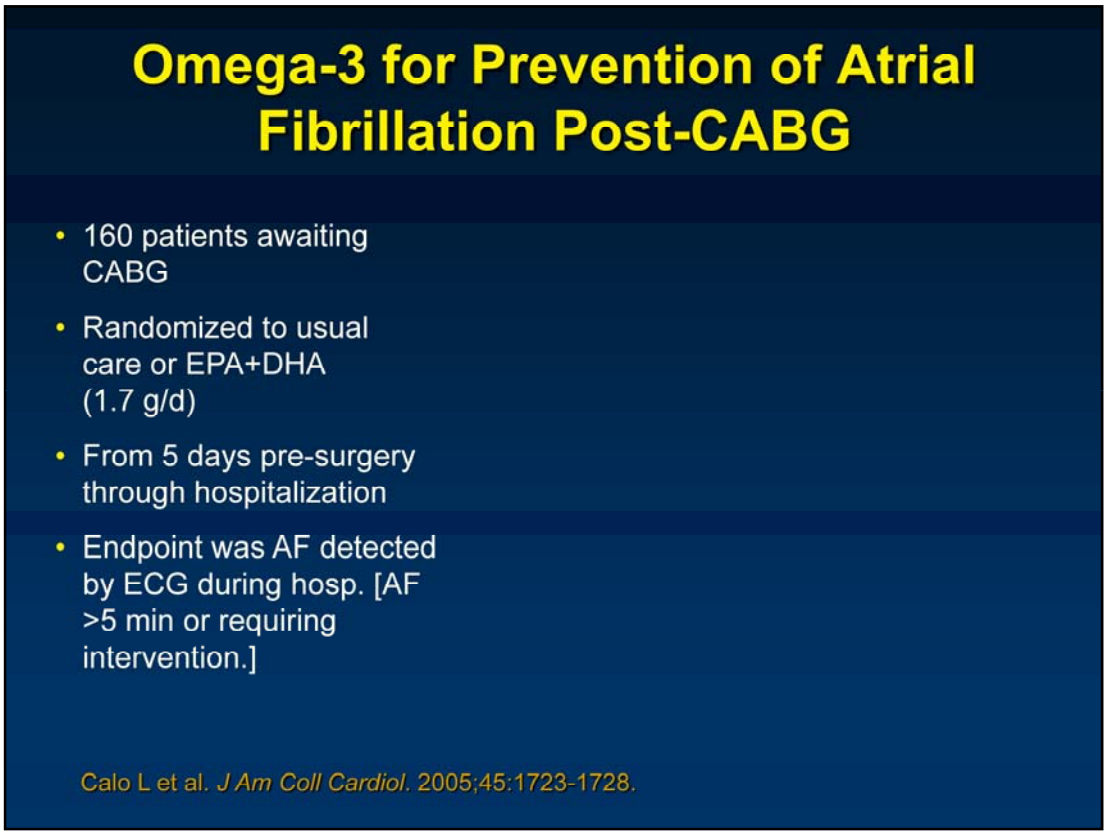




Structural Remodeling

- Structural remodeling is associated with inflammation, fibrosis, apoptosis, etc. consequent to:
  - SHD, age, obesity, genetic factors, etc.
- Drugs that alter the process of atrial stretch, fibrosis, inflammation (remodeling) may also reduce the tendency to develop or progress AF.
- These have included ACE-I's and ARB's (in pts with HTN or HF), statins, and omega-3 fish oil.





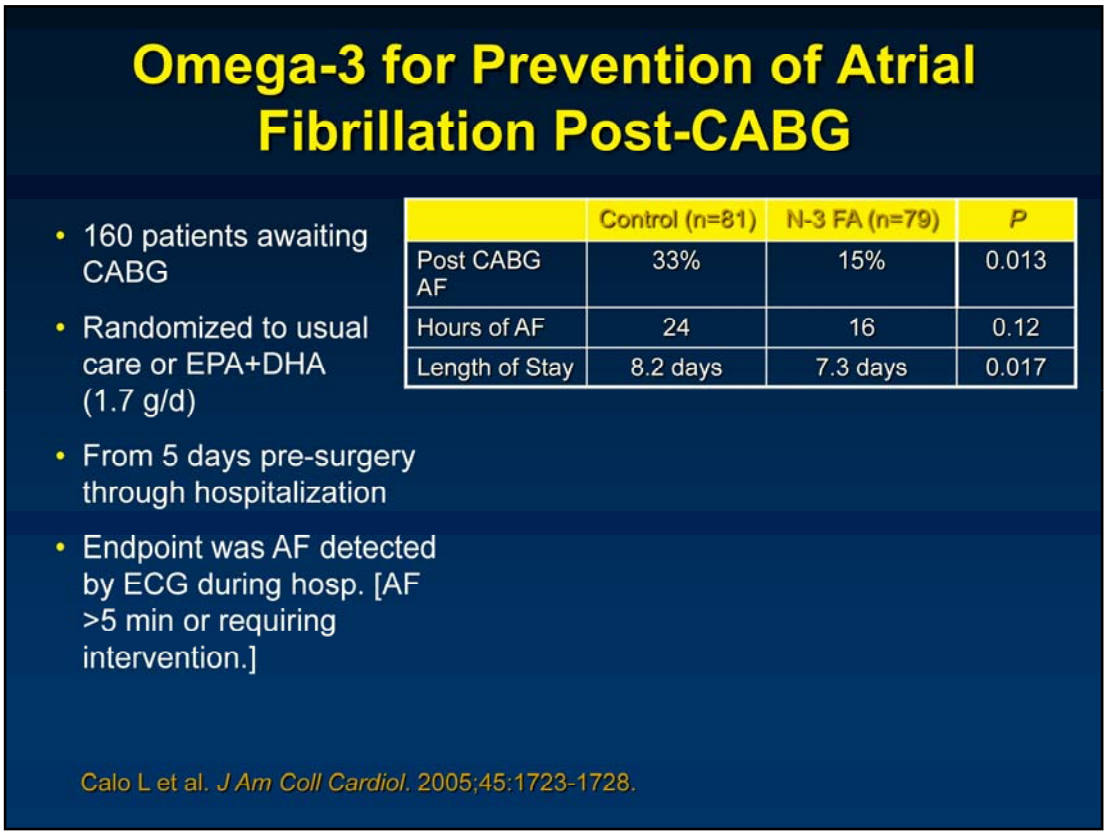
Omega-3 for Prevention of Atrial Fibrillation Post-CABG

In this trial, the use of PUFAs during hospitalization in patients undergoing coronary artery bypass graft surgery (CABG) significantly reduced the incidence of postoperative AF (18.1% absolute risk reduction, 54.4% relative risk reduction) and was associated with a shorter hospital stay. Except for a single case of allergic response, no significant adverse reactions were observed. A possible role of inflammation in the pathophysiology of postoperative AF is suggested, as the anti-inflammatory activity of PUFAs is well-documented.

The graph represents the Kaplan-Meier actuarial estimates of occurrence of postoperative atrial fibrillation in the study group. Atrial fibrillation occurred a mean of 3.2 to 1.1 days after surgery in patients assigned to PUFAs and 3.4 to 1.3 days after surgery in controls (*P*=0.645); AF was diagnosed during continuous electocardiographic monitoring in the intensive or intermediate care units in 11 of 12 (91.6%) patients in the PUFA group and in 25 of 27 (92.5%) patients in the control group (*P*=0.919 by chi-square). The remaining cases of AF (one in the PUFA group and two in the control group) were detected by electrocardiography after the occurrence of symptoms. The mean duration of AF was of 15.5 to 15.8 h in patients assigned to PUFA and 23.9 to 15.3 h in controls (*P*=0.125). Symptoms attributable to AF were reported by 10 of 12 patients (83.3%) in the PUFA group and by 24 of 27 (88.8%) controls (*P*=0.634 by chi-square); AF was initially treated by amiodarone in 9 of 12 patients assigned to PUFA and in 22 of 27 controls (*P*=0.643 by chi-square). Spontaneous conversion to sinus rhythm without any intervention occurred in two patients receiving PUFAs and in three controls (*P*=0.631 by Fisher exact test). Electrical cardioversion was performed on one patient in the PUFA group and in two controls (*P* =0.920 by Fisher exact test). Two of 12 (16.6%) patients in the PUFA group had more than one episode of AF during hospitalization (two episodes and three episodes, respectively), while 5 of 27 (18.5%) patients in the control group had more than one episode of AF (three patients had two episodes and two patients had three episodes) (*P*=0.889 by Fisher exact test).

Reference:

Calo L et al. *J Am Coll Cardiol*. 2005;45:1723-1728.



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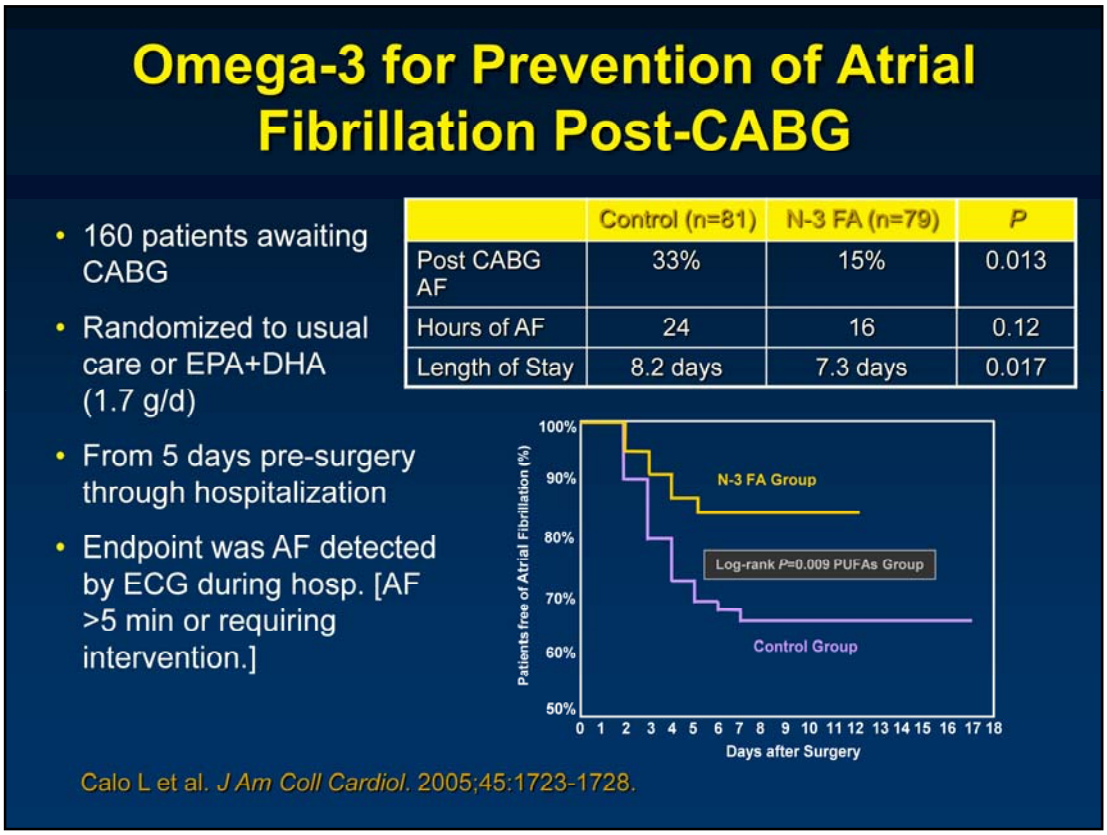

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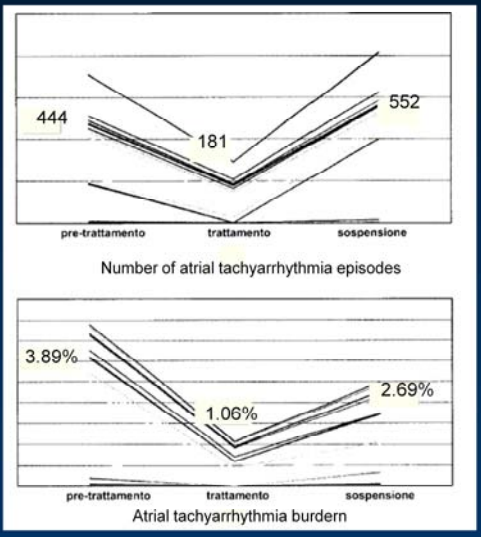
Reduction in AF in Patients with Dual Chamber Pacemakers I



- N=46 (6 not analyzed) with dual chamber PM
- Design—OLX, received 1gm N-3 or nothing for treatment periods of 4 months
- Results
  - 59% reduction in AFib episodes (P=0.037); 67% reduction in AFib burden (P=0.029)
  - P=0.065 and 0.003 for increase in AFib episodes and AFib burden following cessation of therapy
  - For patients with sustained AFib there were similar significant reductions in AFib episodes and AFib burden.

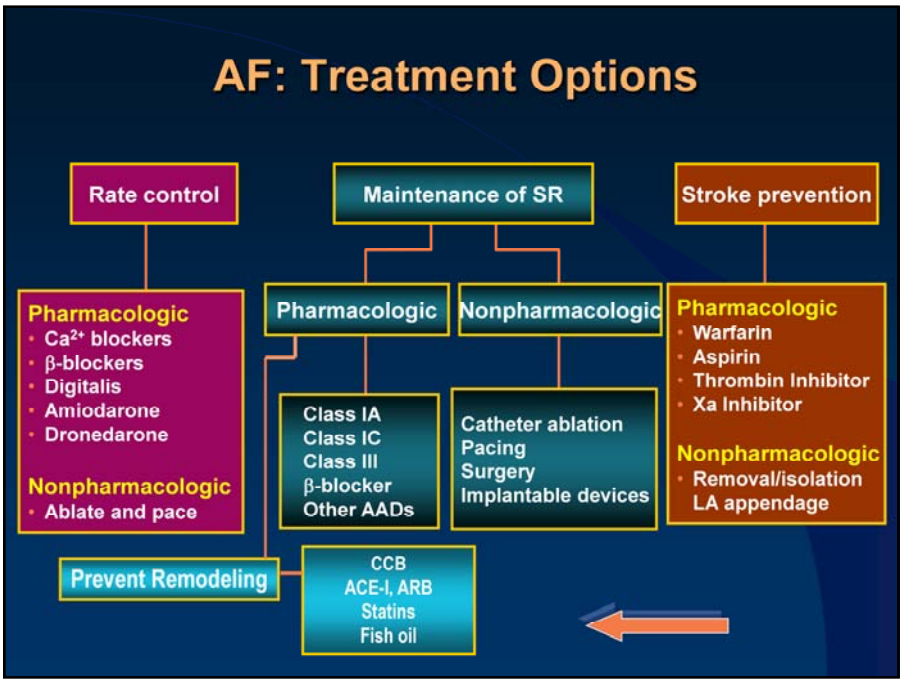
Biscione, et. al, Ital Heart J Suppl Vol 6 Gennaio 2005 (53-59)

Omega-3 for Prevention of Atrial Fibrillation Post-Cardioversion

	Months Post-Cardioversion		
% AFib Rlapses	1	3	6
1 gm Omega-3 daily (N=30)	3.3%	10%	13.3%
Placebo (N=40)	10%	25%	40%
P	0.043	0.004	<0.0001

- 70 consecutive patients with persistent AFib
- Received concurrent amiodarone, beta blockers and RAS inhibitors
- Evaluated with Holter monitor at 1, 3, and 6 months

Nodari, et.al. Euro Heart J 2006, 27 (Abstract Suppl), 887



There are 3 strategies for the management of patients with AF: rate control, maintenance of SR, and stroke prevention. A combination of strategies may be appropriate in some patients.

Rate control is usually easier to achieve than SR maintenance, but the disadvantage is persistence of an irregular ventricular response that does not allow for symptomatic relief for many patients. Although hemodynamic function is improved with rate control, maintenance of SR frequently leads to better results. The drugs (Ca^{2+} blockers, β-blockers, and digitalis) used to maintain ventricular response may cause very slow heart rates in some patients. These patients may require implantation of a permanent pacemaker.

Maintenance of SR has 2 proven advantages, relief of symptoms and improved hemodynamics. In addition, there is the theoretical (but not proven) possibility that maintenance of SR leads to a decrease in thromboembolic events and electrical atrial remodeling. The disadvantage of choosing maintenance of SR as a treatment option is the drug (class IA, IC, and III, β-blockers) side effects, which are usually only an annoyance, but can be life-threatening in a small percentage of patients.

Nonpharmacologic approaches to maintaining SR (MAZE, pulmonary vein isolation) are important adjunctive therapies to consider for patients who are already undergoing cardiac surgery, but are rarely required as first-line therapy. Implantable atrial defibrillators are another nonpharmacologic approach, but substantial patient discomfort and a narrow indication are 2 major disadvantages. Catheter ablation is also an option, and several approaches to this therapy have been reported.

Stroke prevention is important for AF patients with a high risk for stroke. Such patients require warfarin alone or in combination with aspirin as anticoagulation therapy. The nonpharmacologic approach to stroke prevention is LA appendectomy. This can be used as adjunctive or stand-alone therapy and could markedly reduce the risk of embolic stroke and possibly avoid long-term warfarin therapy.

Prystowsky EN. Management of atrial fibrillation: therapeutic options and clinical decisions. *Am J Cardiol*. 2000;85:3D-11D.

AAD Selection for Maintaining NSR in Patients with AF

- Since AF, once rate-controlled and anticoagulated should inherently be a non-lethal arrhythmia, and,
- Since AADs are relatively similar in efficacy for AF,
- The current guidelines for AAD selection for AF focus primarily on safety as the prime selection factor.

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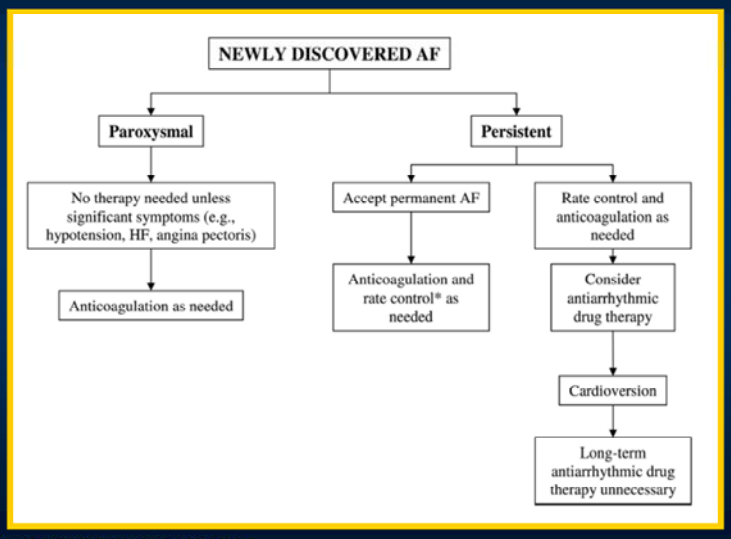
- The current guidelines for AAD selection for AF focus primarily on safety as the prime selection factor.
- *For most pts, AADs are not given following the first episode.*

ACC/AHA/ESC 2006 Guidelines: Pharmacological Management of *Newly Discovered / First Episode* AF



Fuster V, et al. *J Am Coll Cardiol.* 2006;48(4):e149-e246.

Algorithm for AF Therapy (1)

- Permanent AF
  - Anticoagulation and rate control as needed
- Recurrent paroxysmal AF
  - Minimal or no symptoms
    - Anticoagulation and rate control as needed
    - No antiarrhythmic therapy
  - Disabling symptoms in AF
    - Anticoagulation and rate control as needed
    - Antiarrhythmic drug (AAD) therapy
    - AF ablation if AAD therapy fails

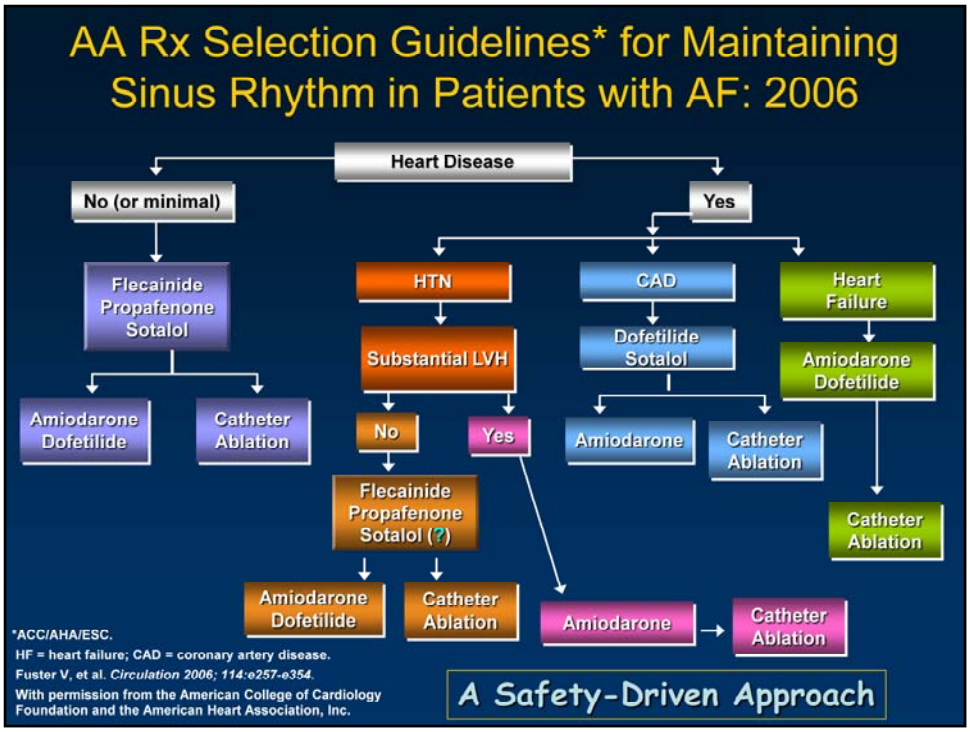
Based upon the 2006 ACC/AHA/ESC guidelines – Fuster V. et al. JACC 2006.

Algorithm for AF Therapy (2)

- Recurrent persistent AF
  - Minimal or no symptoms
    - Anticoagulation and rate control as needed
  - Disabling symptoms in AF
    - Anticoagulation and rate control
    - Antiarrhythmic drug (AAD) therapy *
    - DC cardioversion if needed
    - Continue anticoagulation and therapy to maintain sinus rhythm
    - Consider AF ablation for severely symptomatic recurrence after failure of at least 1 AAD and rate control

* Antiarrhythmic drug for cardioversion and/or for maintenance of sinus rhythm

Based upon the 2006 ACC/AHA/ESC guidelines – Fuster V. et al. JACC 2006.



Antiarrhythmic Drug Selection Guidelines for Sinus Rhythm Control in Patients

with AFib

- **The ACC/AHA/ESC consensus guidelines recommend propafenone as one of the first line treatment options for patients with AFib with no or minimal structural heart disease and those with hypertension with left ventricular hypertrophy <1.4 cm.[1]**

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1. **Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences. *J Am Coll Cardiol*. 2001;38:1266i-1266lxx.**

AAD Selection Issues

- Will it work (efficacy)?
- Will the patient take it (pills never work in the bottle!)?
  - Tolerance, Convenience, Cost
- What is the risk (safety)?
  - Organ toxicity
  - Proarrhythmia
  - Conduction system and inotropic
- Are there dosing / interaction issues?
- Do the guidelines support the decision?

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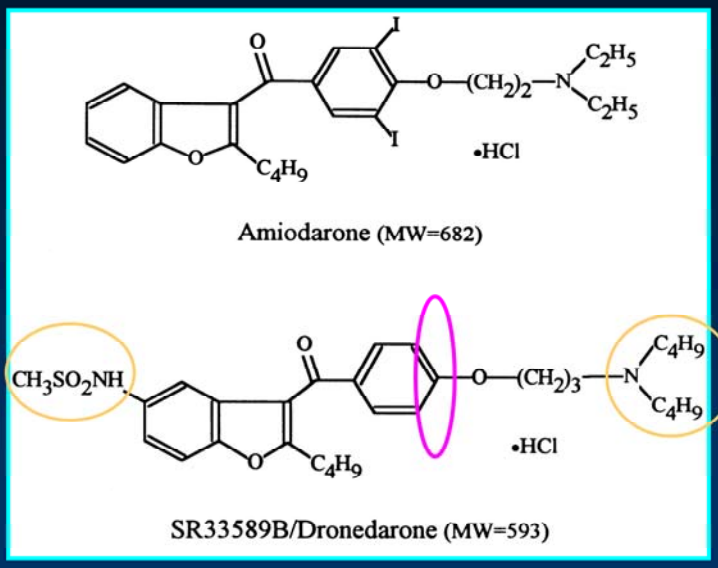
All of our AADs work some/most of the time
but none are perfect !

Dronedarone



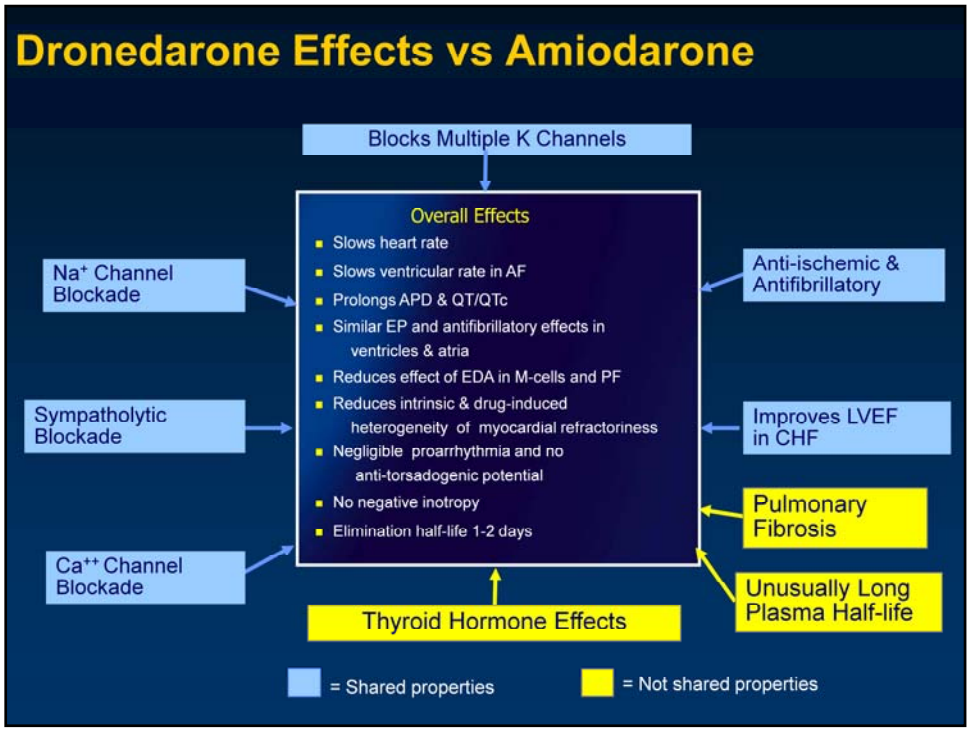
Amiodarone (MW=682)

SR33589B/Dronedarone (MW=593)

Wei Sunet al, Circulation 1999;100:2276-2281

Chemistry and Pharmacologic Profile of Dronedarone

- **Chemical structure**
  - Free of iodine
    - No reported thyroid toxicity
  - Methyl-sulfonamido
    - Low risk of tissue accumulation
- **Pharmacokinetic properties**
  - Half-life: 27–31 hours
  - Low tissue accumulation
- **Mechanism of action**
  - Multi-channel blocker
    - Blocks Ca^{++}, Na^{+}, K^{+} channels
    - Greater atrial specificity *in vitro* than amiodarone
    - Maintains action at increasing heart rates
    - Reduces potential for re-entry
      - Low pro-arrhythmic potential
  - Adrenergic-receptor blocker
    - Rate control


Dronedarone Effects vs Amiodarone
Blocks Multiple K Channels
Overall Effects
Slows heart rate
Slows ventricular rate in AF
Prolongs APD & QT/QTc
Similar EP and antifibrillatory effects in ventricles & atria
Reduces effect of EDA in M-cells and PF
Reduces intrinsic & drug-induced heterogeneity of myocardial refractoriness
Negligible proarrhythmia and no anti-torsadogenic potential
No negative inotropy
Elimination half-life 1-2 days
Na+ Channel Blockade
Sympatholytic Blockade
Ca++ Channel Blockade
Anti-ischemic & Antifibrillatory
Improves LVEF in CHF
Pulmonary Fibrosis
Unusually Long Plasma Half-life
Thyroid Hormone Effects
= Shared properties
= Not shared properties

Dronedarone (Multaq)

- The oral agent closest to approval by the FDA is dronedarone – it received a positive recommendation from the CardioRenal Advisory Committee on 3/18/09
  - Similar to amiodarone but shorter half-life and reduced toxicity
- A dose-finding trial (DAFNE) demonstrating 400 mg bid as the only dose to consider
- A trial demonstrating rate-reduction effects (ERATO)
- Two successful pivotal trials against placebo in AF showing efficacy and safety (EURIDIS and ADONIS)

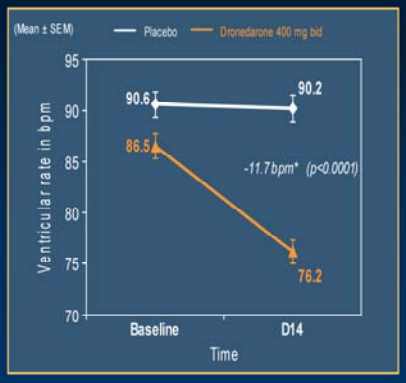
Dronedarone (Multaq)

- One trial in *severe* heart failure (ANDROMEDA) showing excess mortality risk
- One pivotal trial in "high-risk" AF patients (ATHENA) showing efficacy against AF and reduction in CV mortality and hospitalization and in additional endpoints
  THIS IS THE MOST IMPORTANT TRIAL
- One small active-control trial against amiodarone (DIONYSOS) with mixed observations
  - Lower efficacy, better tolerance

The ERATO Rate-Reduction Trial

ERATO: Primary Study End-Point

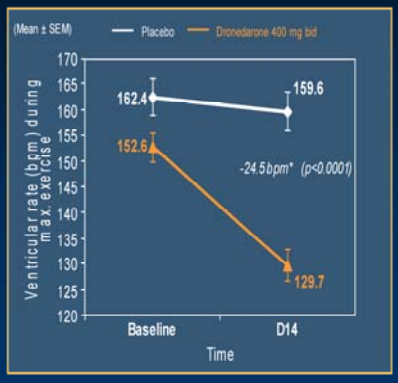
Dronedarone Significantly Decreased Ventricular Rate (24-hour Holter)



*Treatment effect estimate by ANCOVA

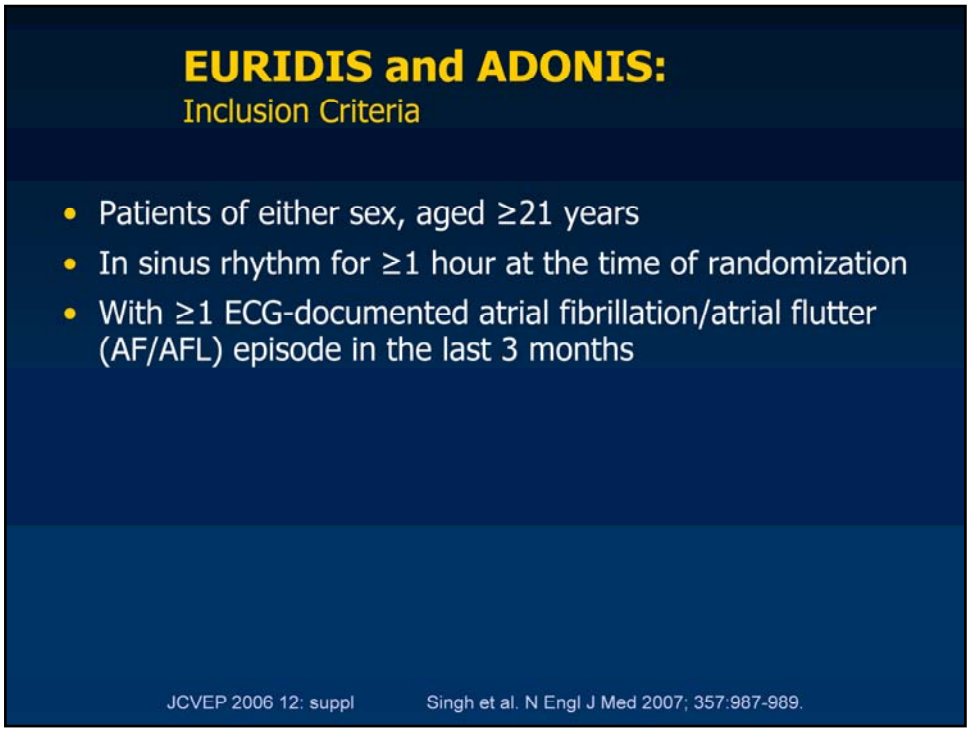
ERATO: Secondary Study End-Point

Dronedarone Significantly Decreased Maximal Exercise Ventricular Rate



*Treatment effect estimate by ANCOVA

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



Eligibility criteria for inclusion in the trials were:

Patients of either sex

Aged ≥21 years

In sinus rhythm for ≥1 hour at the time of randomization

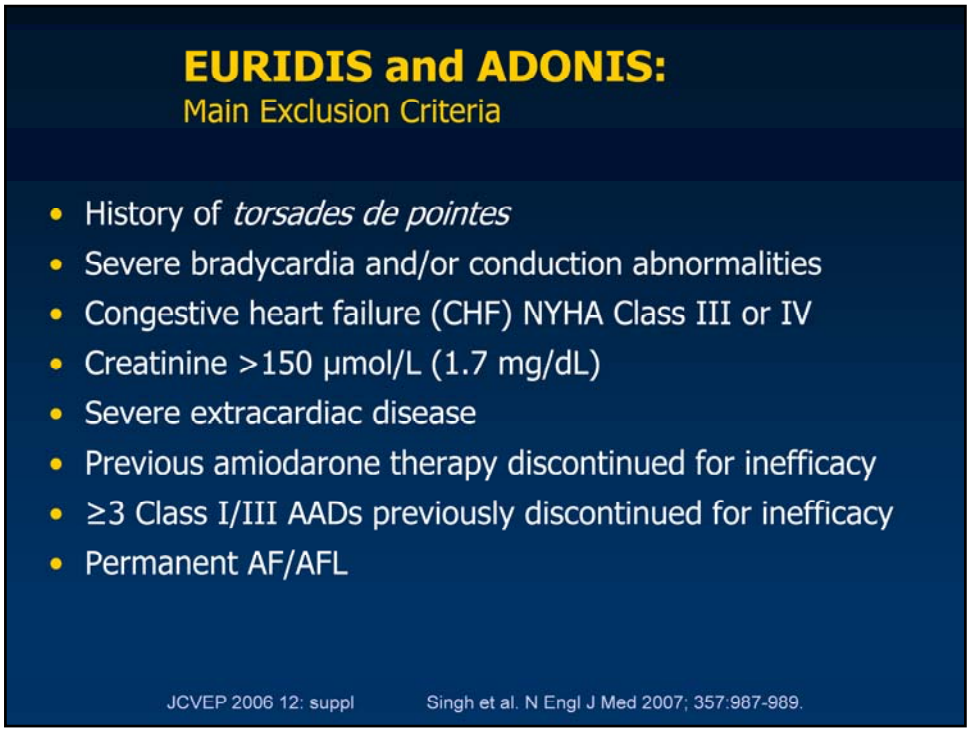
And, with at least one ECG-documented atrial fibrillation/atrial flutter episode in the past three months.

ADONIS: **A**merican-Australian-African trial with **D**ronedar**ON**e **I**n atrial fibrillation or flutter patients for the maintenance of **S**inus rhythm.[1]

EURIDIS: **EUR**opean trial **I**n atrial fibrillation or flutter patients receiving **D**ronedarone for the ma**I**ntenance of **S**inus rhythm.[1]

Reference:

Data on File.



Main exclusion criteria were:

- History of *torsades de pointes*
- Severe bradycardia and/or conduction abnormalities
- Congestive heart failure New York Heart Association class III or IV
- Creatinine >150 µmol/l (1.7 mg/dl)
- Severe extracardiac disease
- Previous amiodarone therapy discontinued for inefficacy
- Three or more class I/III antiarrhythmic drugs previously discontinued for lack of efficacy
- Permanent atrial fibrillation/atrial flutter.

ADONIS: **A**merican-Australian-African trial with **D**ronedar**ON**e **I**n atrial fibrillation or flutter patients for the maintenance of **S**inus rhythm.[1]

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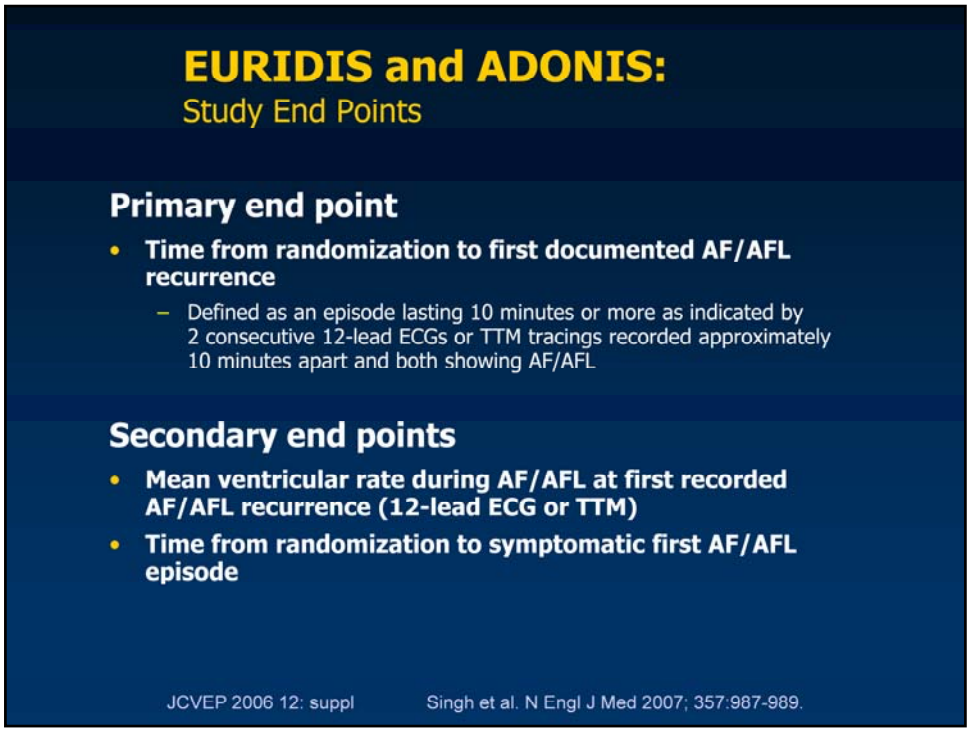

The primary and secondary endpoints in ADONIS and EURIDIS are detailed on this slide.

The primary endpoint selected in this program is well-established and meant to clearly document the antiarrhythmic efficacy of dronedarone:

Time from randomization to first documented atrial fibrillation (AF) or atrial flutter (AFL) recurrence.

defined as an episode lasting 10 minutes or more as indicated by two consecutive 12-lead electrocardiograms (ECGs) or Trans-Telephonic Electro-cardiographic Monitoring (TTM) tracings recorded approximately 10 minutes apart and both showing AF/AFL.

In order to confirm rate control efficacy and effects on symptoms, pre-specified secondary endpoints were defined:

Mean ventricular rate during AF/AFL at first recorded AF/AFL recurrence (12-lead ECG or TTM)

AF/AFL related symptoms at the time of ECG/TTM recording.

ADONIS: **A**merican-Australian-African trial with **D**ronedar**ONE** **I**n atrial fibrillation or flutter patients for the maintenance of **S**inus rhythm.[1]

EURIDIS: **EUR**opean trial **I**n atrial fibrillation or flutter patients receiving **D**ronedarone for the ma**I**ntenance of **S**inus rhythm.[1]

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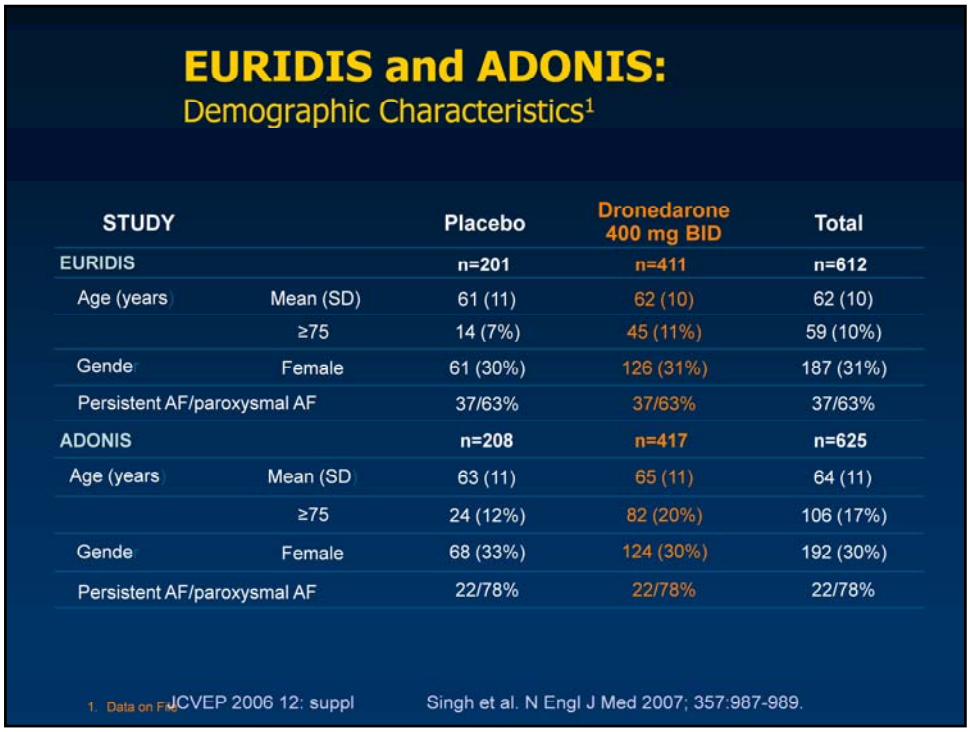

A 2:1 randomization was used to increase the number of patients on dronedarone, thus providing more information on the safety/tolerability profile of the compound.

Baseline characteristics were well balanced between the two trials:

- Mean age 62–64 years
- One third of patients were female
- Similar split between persistent and paroxysmal atrial fibrillation (AF).

These demographics are consistent with those seen in clinical practice and other major clinical trials conducted in AF populations such as in AFFIRM.

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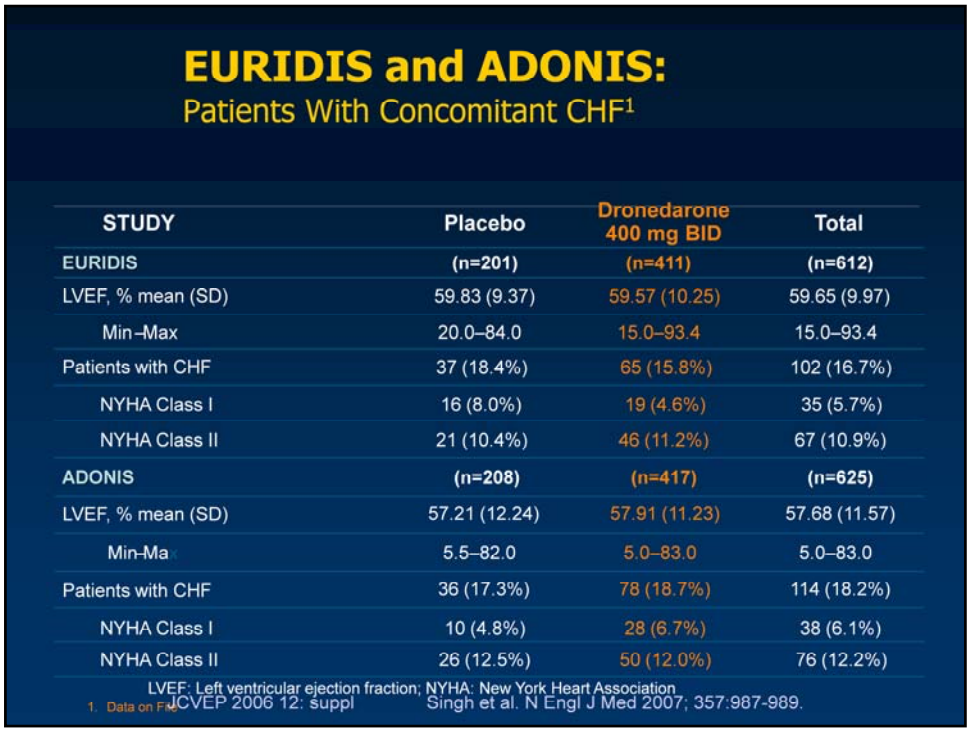

Approximately one in five patients had congestive heart failure (CHF) class I and II in ADONIS and EURIDIS.

Patients with CHF class III and IV were excluded because a specific study examining the efficacy and safety of drondarone in this setting, ANDROMEDA, was planned.

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ANDROMEDA: **AN**tiarrhythmic trial with **DRO**nedarone in **M**oderate to severe CHF **E**valuating morbidity **D**ecre**A**se.[1]

Reference:

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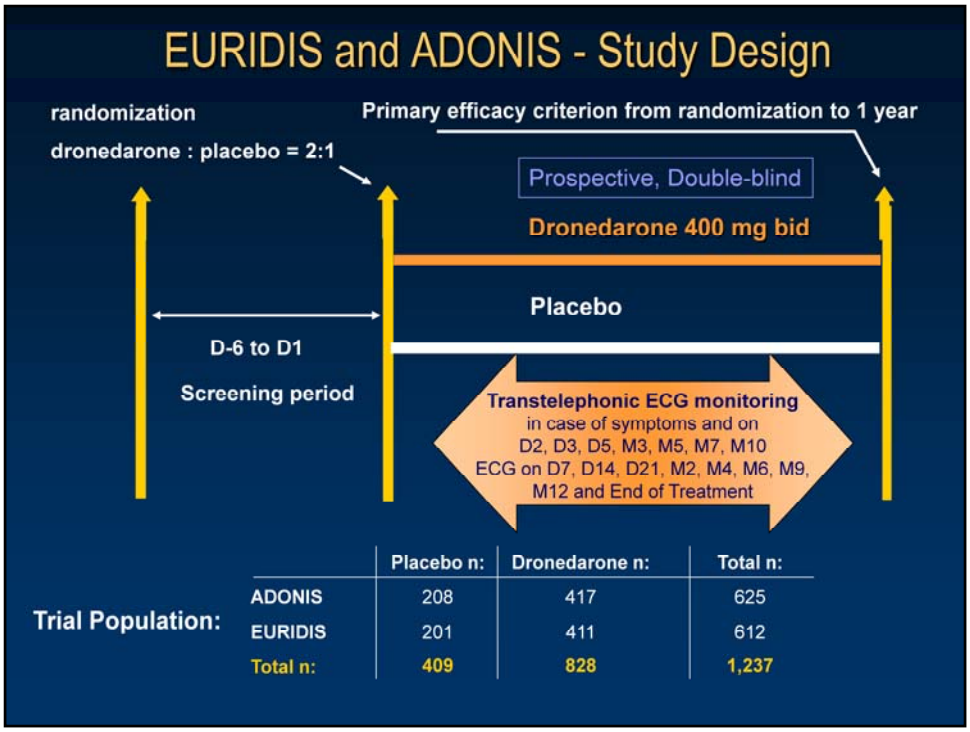

ADONIS and EURIDIS shared the same design and protocol, but were held in different geographic regions; ADONIS in North America, Australia and Africa; EURIDIS in Europe.

In total, the two trials enrolled 1,237 patients with atrial fibrillation (AF) or atrial flutter (AFL).

A 2:1 randomisation was used to increase the number of patients on Dronedarone, thus providing more information on the safety profile of the compound.

To be included in the study, patients had to be in sinus rhythm for ≥1 hour at the time of randomization

Other Eligibility criteria for inclusion in the trials were:

- Patients of either sex
- Aged ≥21 years
- with at least one ECG-documented AF/AFL episode in the past 3 months

Exclusion criteria were

- History of torsades de pointes
- Severe bradycardia and/or conduction abnormalities
- CHF NYHA class III or IV
- Creatinine >150 µmol/l (1.7 mg/dl)
- Severe extracardiac disease
- Previous amiodarone therapy discontinued for inefficacy
- Three or more class I/III AAD previously discontinued for lack of efficacy
- Permanent AF/AFL

ADONIS: American-Australian-African trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm;

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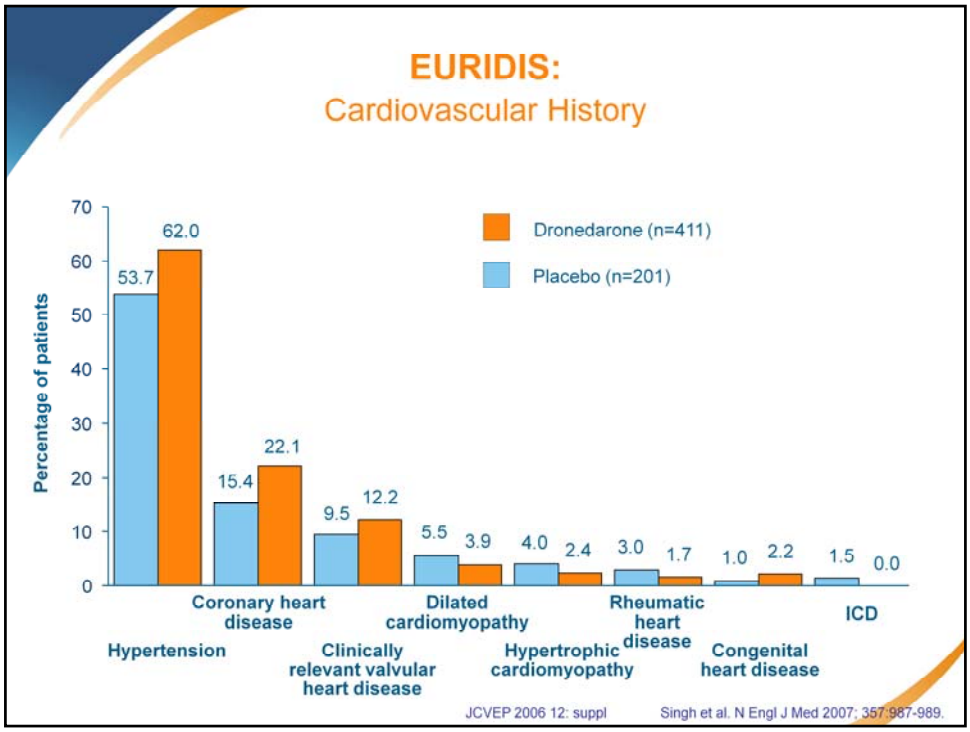

Most patients in EURIDIS and ADONIS suffered concomitant cardiovascular disorders, as detailed on this slide.

Hypertension was the most common concomitant disorder, experienced by more than half of all patients in the two studies.

One in five patients had coronary heart disease.

These data are worth considering given the clinical importance of underlying heart disease in atrial fibrillation patients.

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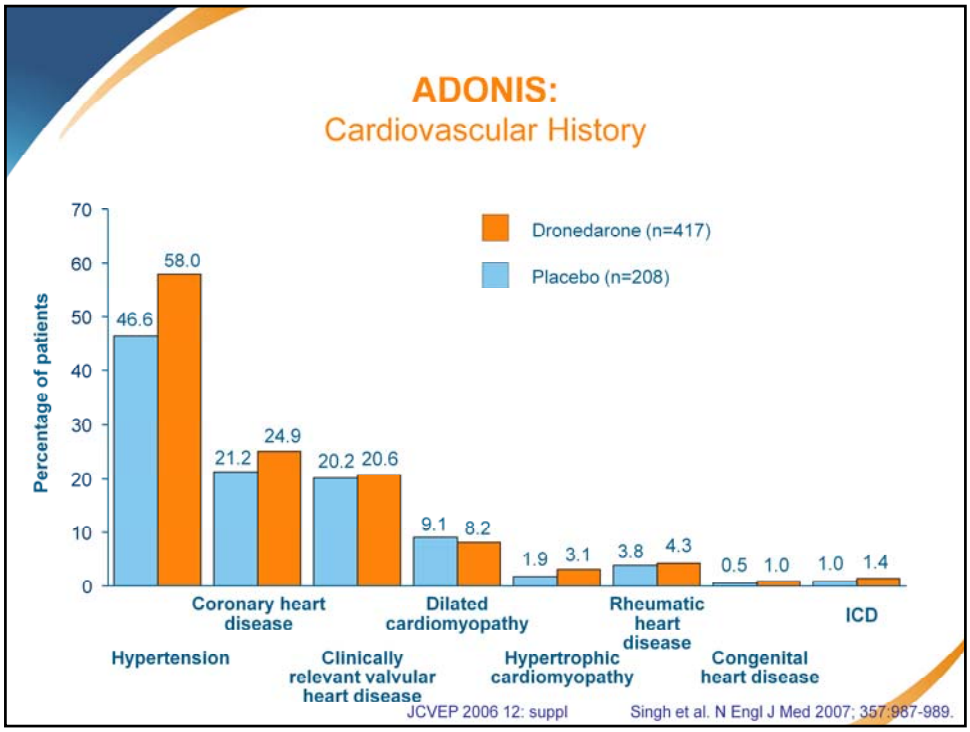

Similar cardiovascular history was observed in ADONIS patients.

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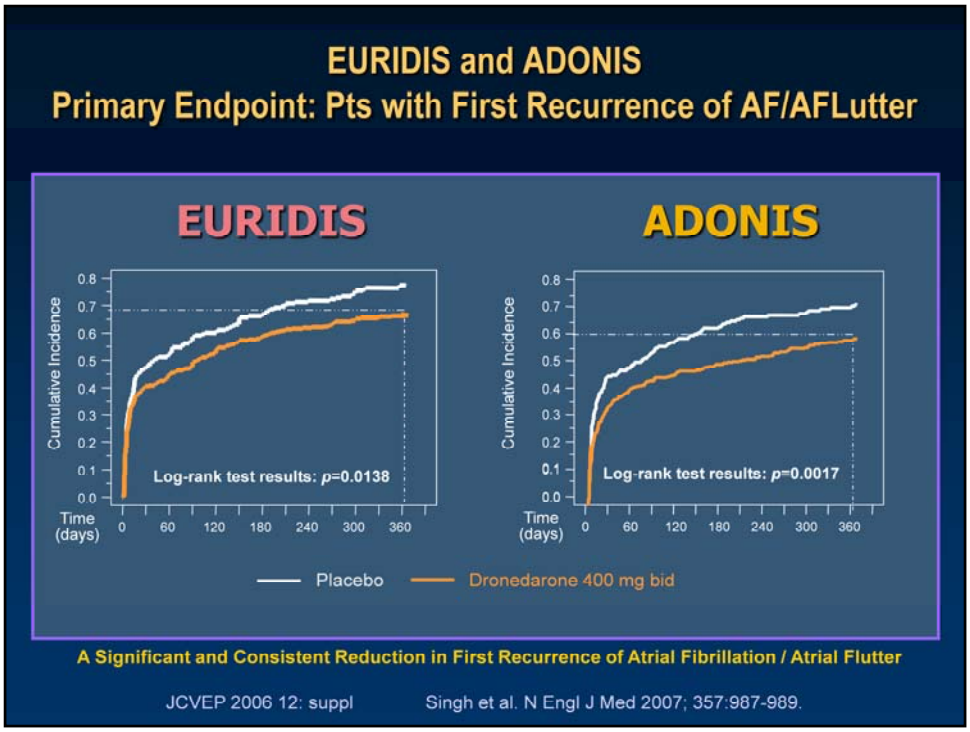

These two Kaplan–Meier curves illustrate the significant reduction in the relative risk of first recurrence of atrial fibrillation (AF) or atrial flutter (AFL) observed with dronedarone compared with placebo in the ADONIS and EURIDIS trial. Included in these recurrences are asymptomatic events as reported by the regular Trans-Telephonic Electro-cardiographic Monitorings (TTEMs), which were part of the studies' protocol.

ADONIS and EURIDIS show that dronedarone is highly effective in the prevention of AF and AFL recurrences:

- ADONIS yielded a 27.5% reduction in the relative risk of recurrence in favor of dronedarone compared with placebo (p=0.0017).
- The relative risk reduction observed in EURIDIS was 21.6% in favor of dronedarone compared with placebo (p=0.0138).
- Median time from randomization to a first adjudicated recurrence of AF/AFL was 2.3 times longer in the dronedarone group compared with placebo.

Results from the 2 studies are remarkably consistent

ADONIS: **A**merican-Australian-African trial with **D**ronedar**ON**e **I**n atrial fibrillation or flutter patients for the maintenance of **S**inus rhythm;

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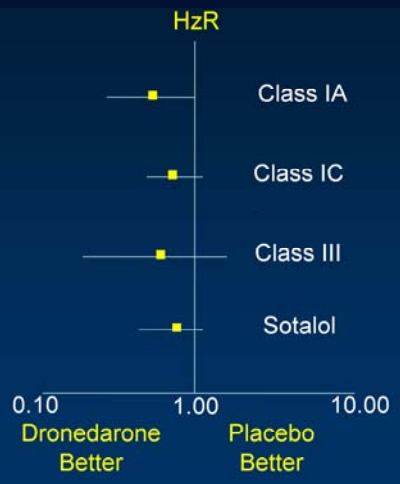
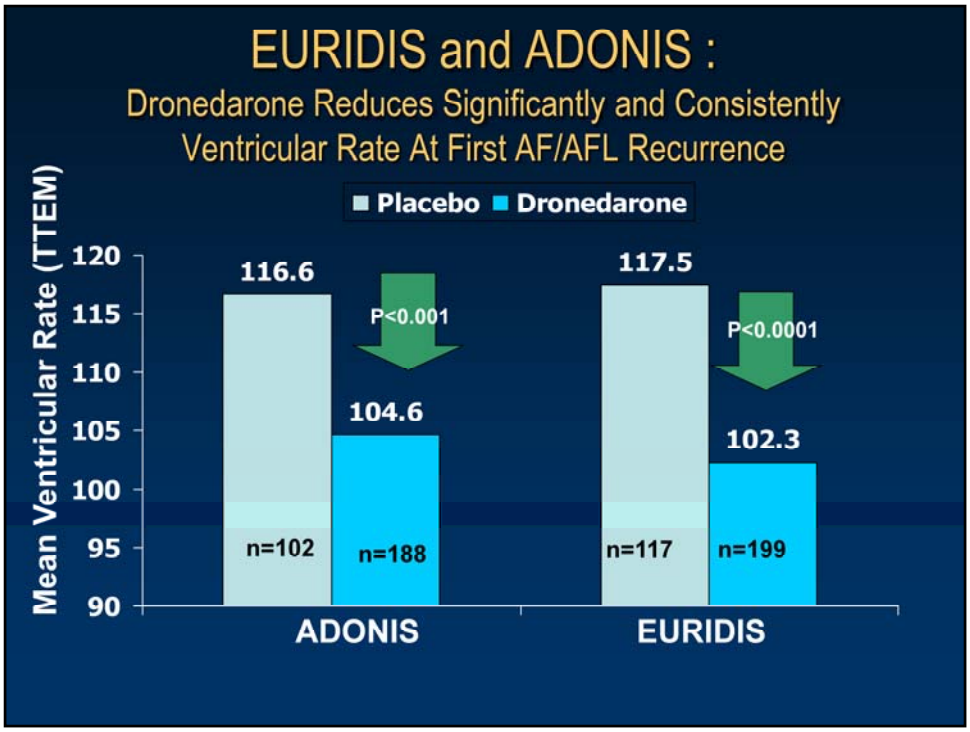
EURIDIS and ADONIS: Outcomes in Patients Who Failed Prior AAD Rx

- A post-hoc analysis was performed to evaluate the efficacy of dronedarone in reducing AF recurrences in pts who had failed at least one prior AAD due to inefficacy.
- Dronedarone trended towards superior to placebo in each subgroup of pts: 41 who failed a class IA drug, 170 who failed a class IC drug, 160 who failed sotalol, and 45 who failed another class III drug.



Singh et al. Circulation 2006; 114 (suppl II) II-790



Data from ADONIS and EURIDIS show that in addition to being consistently effective in the reduction of the relative risk of recurrence of atrial fibrillation (AF) and atrial flutter (AFL), and maintaining sinus rhythm, dronedarone significantly decreases the ventricular rate during the first recurrence of AF / AFL:

- Mean ventricular rate reduced to 104.3 bpm with dronedarone compared with 116.6 bpm with placebo in ADONIS ($p<0.001$);
- Mean ventricular rate reduced to 102.3 bpm with dronedarone compared with 117.5 bpm with placebo in EURIDIS ($p<0.0001$).
- This rate control effect might be the key factor explaining the better control of AF symptoms with dronedarone.

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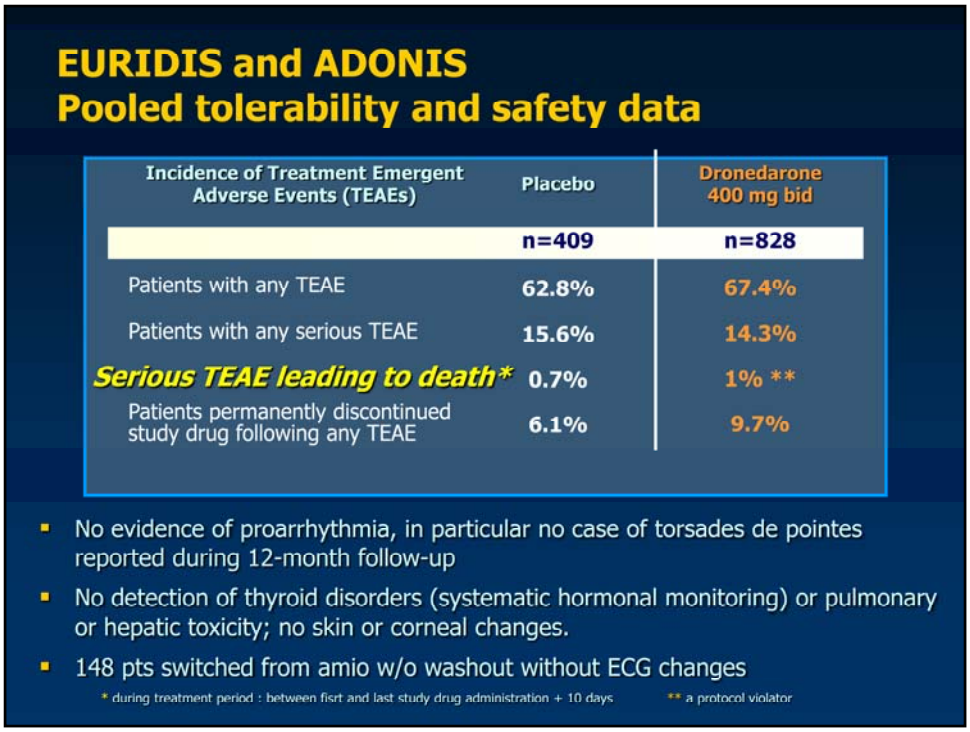

A 2:1 randomisation was used to increase the number of patients on Dronedarone, thus providing more information on the safety profile of the compound.

Separate as well as pooled data from the EURIDIS and ADONIS trials show that the safety profile of dronedarone is similar to that of placebo.

Dronedarone treatment was associated with fewer incidences of serious AEs (SAEs) compared with placebo (19.8% vs. 24.4%, respectively);

Furthermore, dronedarone treatment was associated with fewer incidences of drug-related SAEs compared with placebo

The incidence of deaths was low and similar in the two groups.

No evidence of proarrhythmia, in particular no torsades de pointes, was reported during the 12-month follow-up period.

ADONIS: American-Australian-African trial with DronedarONe In atrial

ANDROMEDA

- **A mortality trial conducted in a patient group outside the targeted AF indication:**
  - To assess the potential benefit of dronedarone in reducing mortality and CHF hospitalizations in patients with severe CHF (III/IV)
  - To confirm the absence of adverse effect on mortality and the non pro-arrhythmic profile in a population at high mortality rate and high risk of developing torsades de pointes
  - To further assess the safety profile of dronedarone

Kober L et al. NEJM 2008; 358:2678-87.

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  - To further assess the safety profile of dronedarone

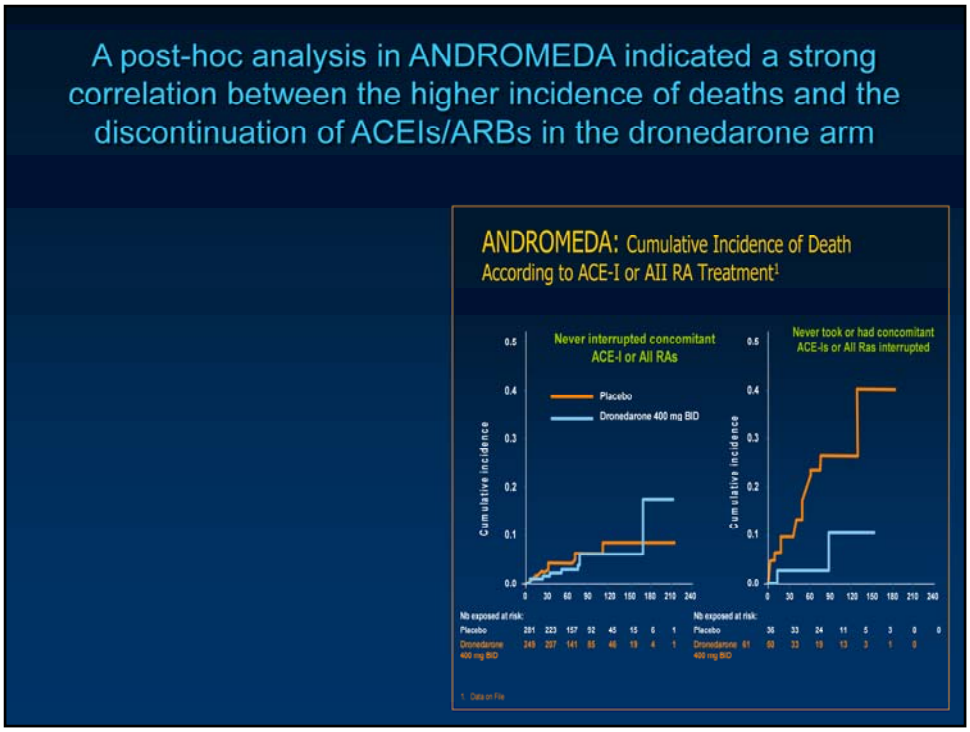
Primary end-point : time to death or hospitalization for worsening heart failure

	Placebo N= 317	Dronedarone 400 mg bid N = 310
No. of pts with end-point	40	53
RR	1.38	
95% CI	(0.918-2.088)	
Log-rank's test result (p value)	0.118	

All Cause Mortality: Placebo n=12, Dronedarone n=25
HzR 2.13, p=0.03

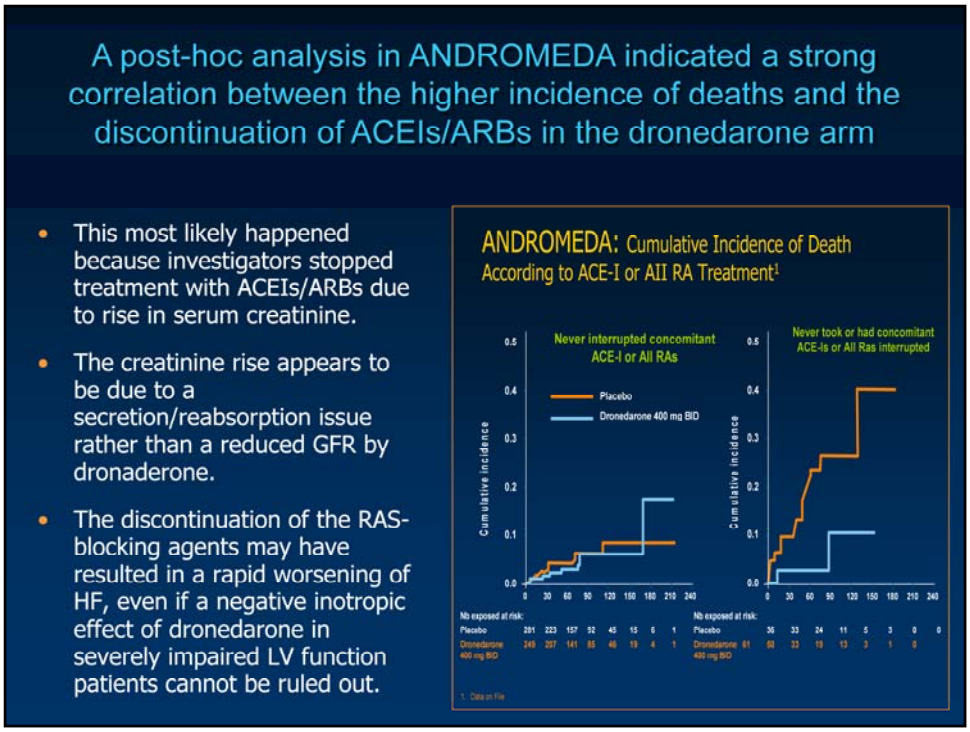
Kober L et al. NEJM 2008; 358:2678-87.

No TdP was noted in ANDROMEDA.



Preliminary conclusions from ANDROMEDA are that :

- Dronedarone was not superior to placebo in reducing mortality or decreasing the rate of CV hospitalizations in a population of patients with advanced heart failure;
- An excess of mortality was observed in the dronedarone arm, mainly non-sudden deaths, most often in relation to worsening heart failure;
- A post-hoc analysis indicates a strong correlation between the higher incidence of deaths and the discontinuation of ACEIs/ARBs in the dronedarone arm;
  - This might have happened because investigators stopped treatment with ACEIs/ARBs due to rise in serum creatinine;
  - The discontinuation of the RAS-blocking agents may have resulted in a rapid worsening of HF, even if a negative inotropic effect of dronedarone in severely impaired LV function patients cannot be ruled out as a precipitating factor in patients with low ejection fraction
- Importantly, no torsades de pointes were reported, confirming the non pro-arrhythmogenic profile of dronedarone, even in a highly susceptible population;
- No definitive conclusions regarding overall cardiac safety of dronedarone in CHF patients can be drawn from the ANDROMEDA results. In particular, patients with heart failure with preserved systolic function were not included in the study and represent a significant proportion of CHF patients;
- For these reasons, a new Morbidity and Mortality study, ATHENA, will be conducted to definitively establish the benefits of dronedarone in high-risk patients with AF and to confirm the good cardiac and extra-cardiac safety of Dronedarone already observed in DAFNE, EURIDIS, ADONIS and ERATO.



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ATHENA: A High-Risk AF Trial

- 4628 pts with AF and:
  - Age 75 or more, or
  - Age 70 plus 1 risk factor (HTN, DM, CVA/TIA, LA 50 mm or more, LVEF 40% or less)
    - Initially younger pts with risk markers were allowed but an appendix early in the trial changed the lowest age to 70
    - Only 6% had lone AF; class IV HF was excluded
- Dronedarone 400 mg bid or placebo given in a prospective, randomized, double-blinded trial with minimum f/u 1 yr and a primary efficacy endpoint of TM/1st CV hospitalization.

ATHENA: Trial Objectives

- **Primary objective:**
  - Time to first hospitalization due to cardiovascular events or death from any cause
- **Secondary objectives:**
  - Death from any cause
  - Death from cardiovascular causes
  - First hospitalization due to cardiovascular events
- **Additional analyses performed included:**
  - Effects on AF
  - Effects on other CV endpoints
  - Effects on stroke

Hohnloser, SH et al. *NEJM.* 2009;360:668-78.

In ATHENA Dronedarone:

- **Reduced TM/1st CV hospitalization**
  - HzR 0.76, p<0.001
  - Trend towards reduced TM

    HzR 0.84, p=0.176
- **Reduced 1st CV hospitalization**
  - HzR 0.75, p<0.001
- **Reduced CV death**
  - HzR 0.71, p=0.034
- **Reduced Arrhythmic death**

  HzR 0.55, p=0.01

In ATHENA Dronedarone:

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  - Trend towards reduced TM
    HzR 0.84, p=0.176
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- **Reduced CV death**
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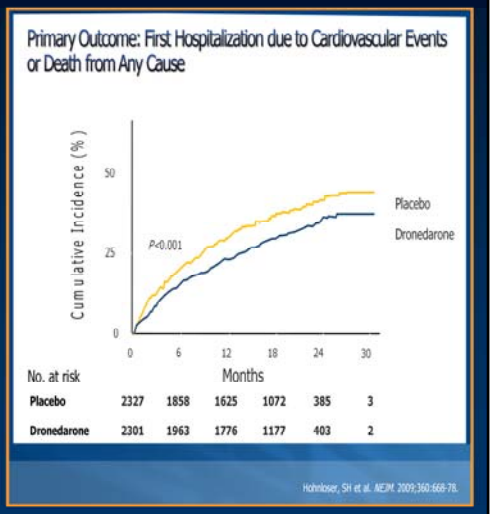
- **Reduced Arrhythmic death**
  HzR 0.55, p=0.01



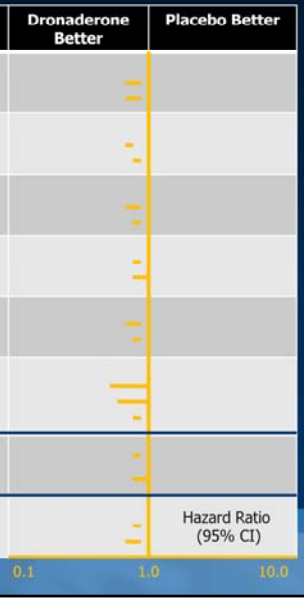
In ATHENA

• Total Mortality:	Dronedarone	Placebo
	116	139
CV	63	90
Non-CV	49	53
CV non-Arr	17	18
CV Arr	26	48

- The decrease in hospitalization was mainly due to:
  - Decreased AF: p<0.001
  - Decreased ACS: p=0.030
  - Decreased non AF/AFl CV hosp: HzR 0.86, p=0.02*

ATHENA: Results by Selected Baseline Characteristics

Characteristic	Patients (no/total no)
Age	
≥75 yr	942/2703
≤ 75 yr	709/1925
Gender	
Male	850/2459
Female	801/2169
Presence of AF or flutter	
Yes	396/1155
No	1255/3473
SHD	
Yes	1115/2732
No	524/1853
Any Congestive Heart Failure	
Yes	603/1365
No	1048/3263
LVEF	
<35%	86/179
35 to <45%	145/361
≥45%	1387/4004
Use of ACEI or ARB	
Yes	1175/3216
No	476/1412
Use of beta-blocker	
Yes	1226/3269
No	425/1359



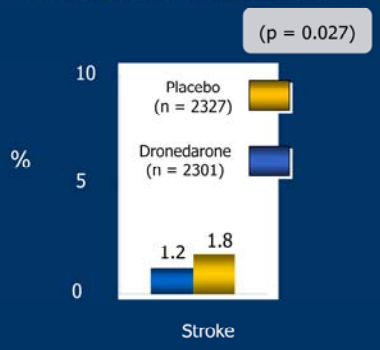
In ATHENA:

- Discontinuations were similar for dronedarone (30.2%) and placebo (30.8%).
- Discontinuations for AE's were 12.7% for dronedarone and 8.2% for placebo.
  - For dronedarone, most were for GI symptoms.
  - For placebo, most were for AF recurrence.
  - There were no differences in AE's re: skin, pulmonary, thyroid.
- 4% on dronedarone showed an increase in serum [creatinine]
  - There were no excess withdrawals of ACEI/ARBs

ATHENA Update September 2008

Trial design: High-risk patients with paroxysmal or persistent atrial fibrillation or flutter were randomized to dronedarone 400 mg twice daily or placebo. Patients were followed for a mean of 21 months.

Dronedarone reduced stroke 34% *



- The significant reduction in stroke was incremental to background anti-thrombotic therapy
- Similar to the primary endpoint, it appeared early and was maintained during follow-up.

www.cardiosource.com

* Stroke data presented at ESC 9/3/08, Hohnloser S. et al.

Dronedarone: Impression

- An effective agent for AF as compared to placebo, in a wide variety of patients.
- A single dosing regimen: 400 mg bid.
- A good safety and tolerance profile at this dose without significant organ toxicity in trials up to 3 yrs of follow up.
- Minimal drug interactions to date, but effect on serum creatinine must be kept in mind.
- Clinically important benefits in “high-risk” AF patients (without severe HF), that may set a new standard for antiarrhythmic drug development.

ATHENA Summary

- ATHENA is the largest trial for AF to date
- Results show dronedarone significantly prolongs the time to AF recurrence compared with placebo
- No significant difference was found between placebo and dronedarone in all-cause mortality
- However, dronedarone reduced CV mortality, CV hospitalizations, ACS, arrhythmic deaths, stroke, etc. [A significant marketing issue.]
- Adverse events occurring significantly more frequently with dronedarone than with placebo included bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level
- However, total discontinuation rates for dronedarone and placebo were identical and there was no pulmonary or thyroid toxicity evident and no TDP/VF deaths in this "high-risk" AF population in dronedarone-treated patients

DIONYSOS

- An active-control trial required by the European Union's approval process.
- 504 pts with:
  - Persistent AF (>72 hrs; for whom CV and AAD Rx was indicated; all were anticoagulated)
  - Studied in a short-term, randomized, double-blind, parallel group study. [Mean f/u was 7 months]
- Dosing:
  - Dronedarone 400 mg bid
  - Amiodarone 600 mg/d for 4 wk than 200 mg/d
- *Dronedarone was less effective but better tolerated than amiodarone*

Press Release 12/23/08

DIONYSOS

- **Primary efficacy endpoint:** recurrent AF following DC cardioversion or premature drug discontinuation for intolerance or lack of efficacy:
  - Dronedarone 73.9%, Amiodarone 55.3% ($p<0.001$)
    - Recurrent AF:
      Dronedarone 36.5%, Amiodarone 24.3%
    - Drug discontinuation:
      Amiodarone 34 patients, Dronedarone 26 patients

Press Release 12/23/08

DIONYSOS

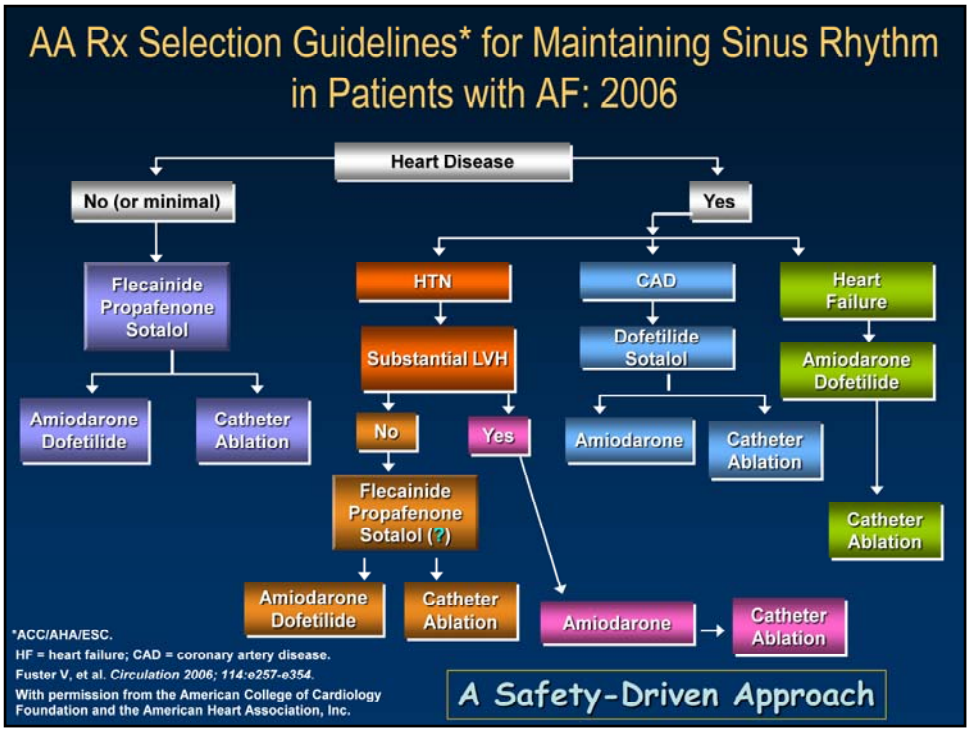
- **Primary safety endpoint:** thyroid, hepatic, pulmonary, neurological, skin, occular, GI adverse events and premature drug discontinuation for an AE:
  - Dronedarone 83 patients, Amiodarone 107 patients (a 20% reduction in favor of dronedarone) (p=0.1291)
  - Dronedarone had fewer thyroid (2 vs 15), neurological (3 vs 17), and premature drug discontinuation for AEs (13 vs 28) events but more GI events (32 vs 13). This was consistent with expectations from prior trial data
  - Dronedarone also had less bradycardia (8 vs 22) and less pronounced QT prolongation (27 vs 52)
  - There was no TdP noted in the trial
  - While the trial was not designed to assess mortality, there were fewer deaths on dronedarone (2) than on amiodarone (5)

Press Release 12/23/08

Ranolazine

- Ranolazine has been identified as an inactivated state sodium channel blocker with little effect on peak INa in ventricular and some in atrial myocardium.
- Ranolazine also blocks I_{Kr}, and can prolong the QT interval.
- Studies performed in-vivo have suggested potential for the prevention of AF.
- Data to date in humans indicates ventricular and atrial antiarrhythmic potential in ischemic patients.
- Its effects in the MERLIN trial and its antiarrhythmic EP properties are now listed in its package insert.
- AF trials are under development

*Antzelevitch et al. ISHNE AF Worldwide Internet Symposium II, 2007
http://www.af-symposium.org/2007



Antiarrhythmic Drug Selection Guidelines for Sinus Rhythm Control in Patients

with AFib

- **The ACC/AHA/ESC consensus guidelines recommend propafenone as one of the first line treatment options for patients with AFib with no or minimal structural heart disease and those with hypertension with left ventricular hypertrophy <1.4 cm.[1]**

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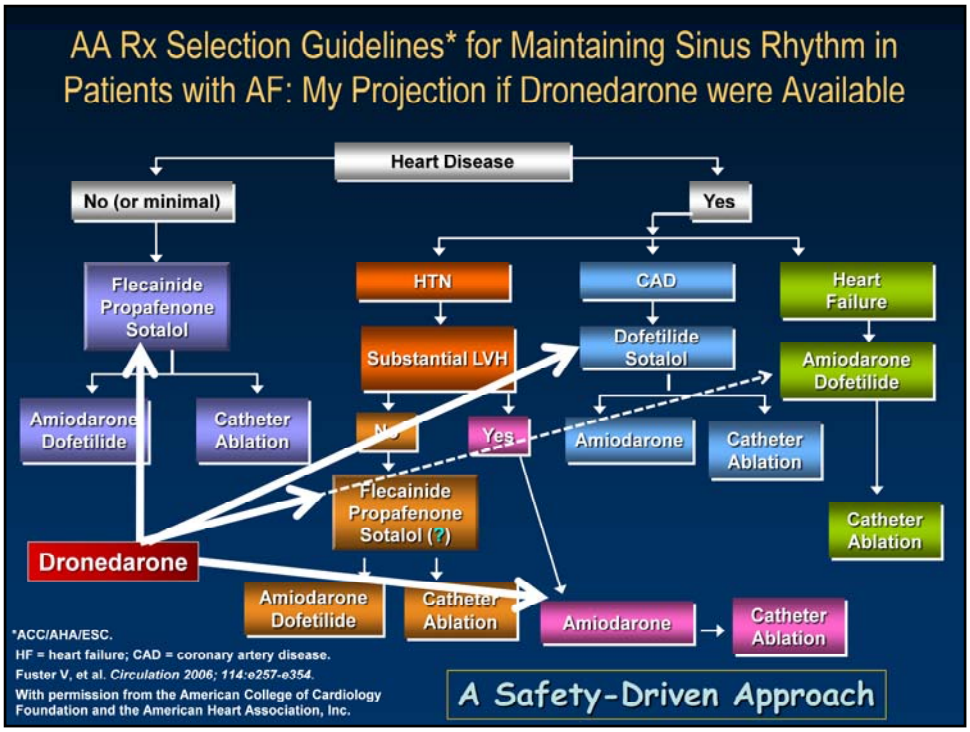
1. **Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences. *J Am Coll Cardiol*. 2001;38:1266i-1266lxx.**



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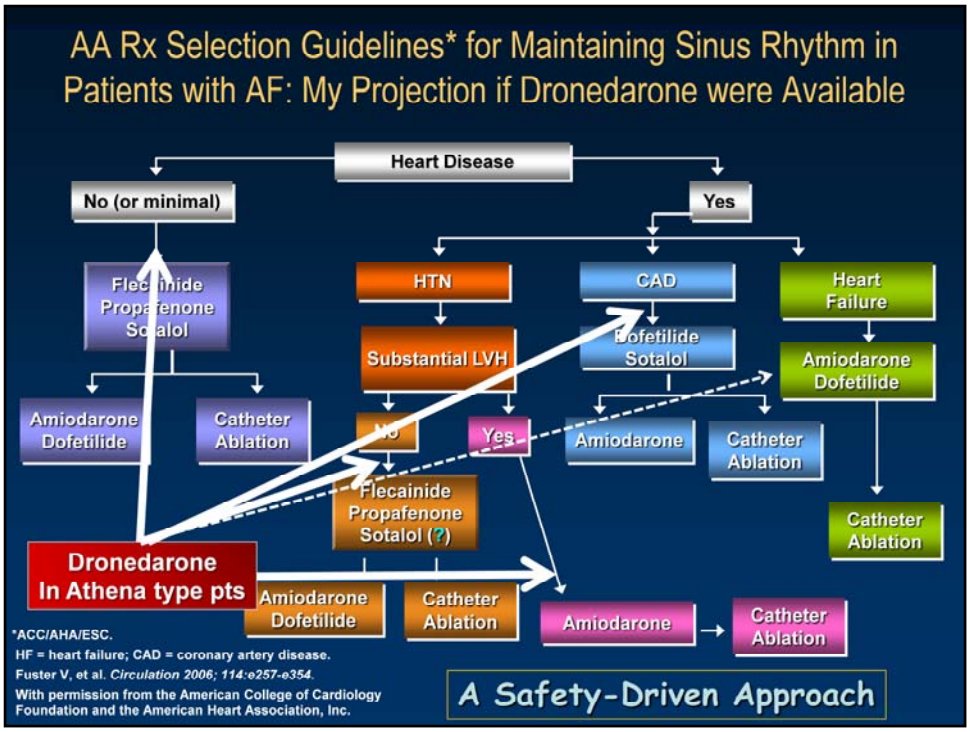

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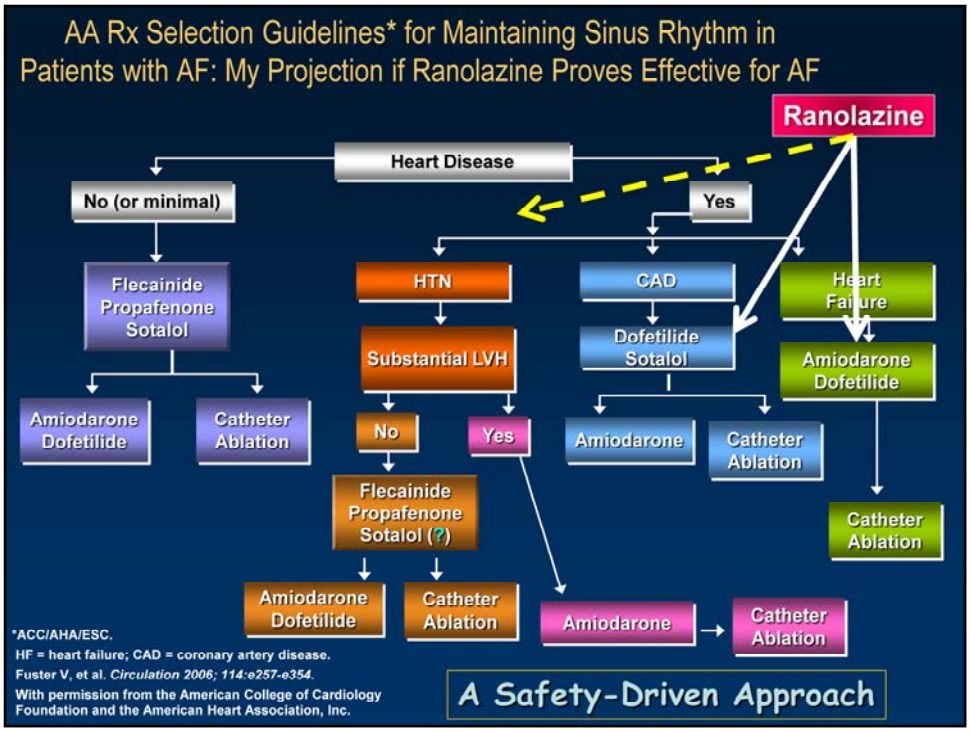
1. **Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences. *J Am Coll Cardiol*. 2001;38:1266i-1266lxx.**



Antiarrhythmic Drug Selection Guidelines for Sinus Rhythm Control in Patients

with AFib

- **The ACC/AHA/ESC consensus guidelines recommend propafenone as one of the first line treatment options for patients with AFib with no or minimal structural heart disease and those with hypertension with left ventricular hypertrophy <1.4 cm.[1]**

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1. **Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences. *J Am Coll Cardiol*. 2001;38:1266i-1266lxx.**

Other Investigational Antiarrhythmics Now Under Study For Atrial Fibrillation Conversion and/or Control:

"Atrial-Specific" Agents

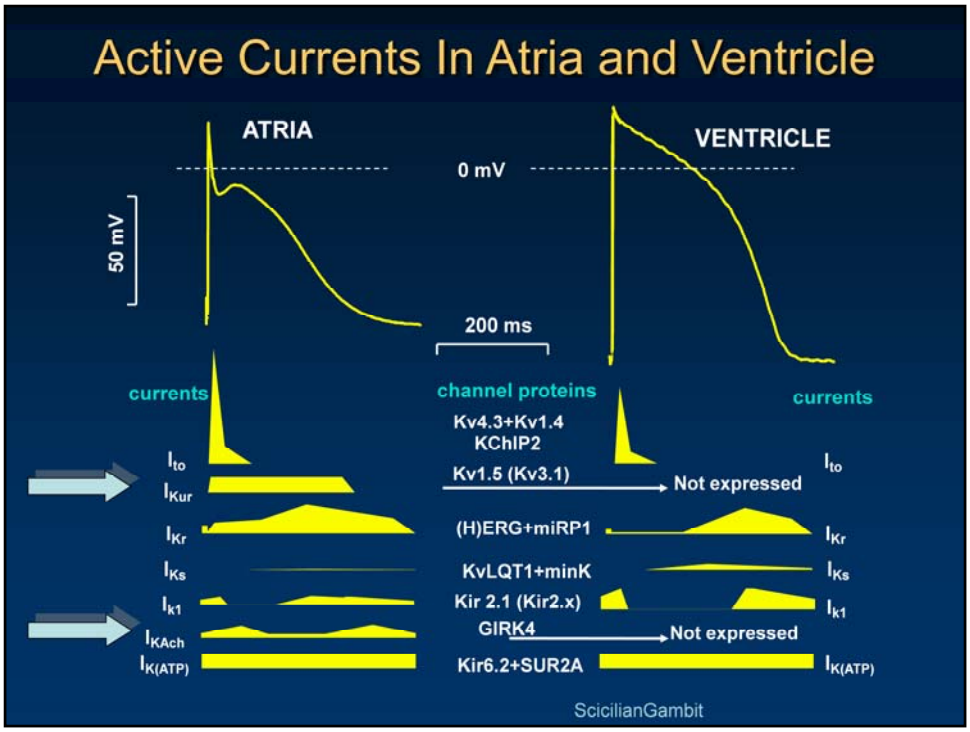
- RSD-1235 (I_{Kur}; I_{to}; I_{Na}; I_{KACH})
- *AVE0118 (I_{Kur}; I_{to}; I_{KACH})*
- *AVE1231* ($I_{Kur;}$ +)
- AZD7009 (I_{Kr}; I_{Kur}; I_{Na})
- C9356 ($I_{Kur;}$ +)
- NIP142 (I_{Kur}; I_{KACH})
- NIP151 (I_{KACH})
- MPS (I_{Kur})
- JTV-519 (I_{KACH}, I_{Kr})
- S1185, S0100176, S9947, S20951 ($I_{Kur;}$)
- Piboserod (5-HT_4 receptor antagonist)
- Ranolazine (late I_{Na}, I_{CaL}, I_{Kr}, I_{Na-Ca} in vent, peak I_{Na} in atria)
- Acacetin (I_{Kur}; I_{to}; I_{KACH}) *(a Chinese Herb Derivative)*
- *Compound A (BMS)* (I_{kur})

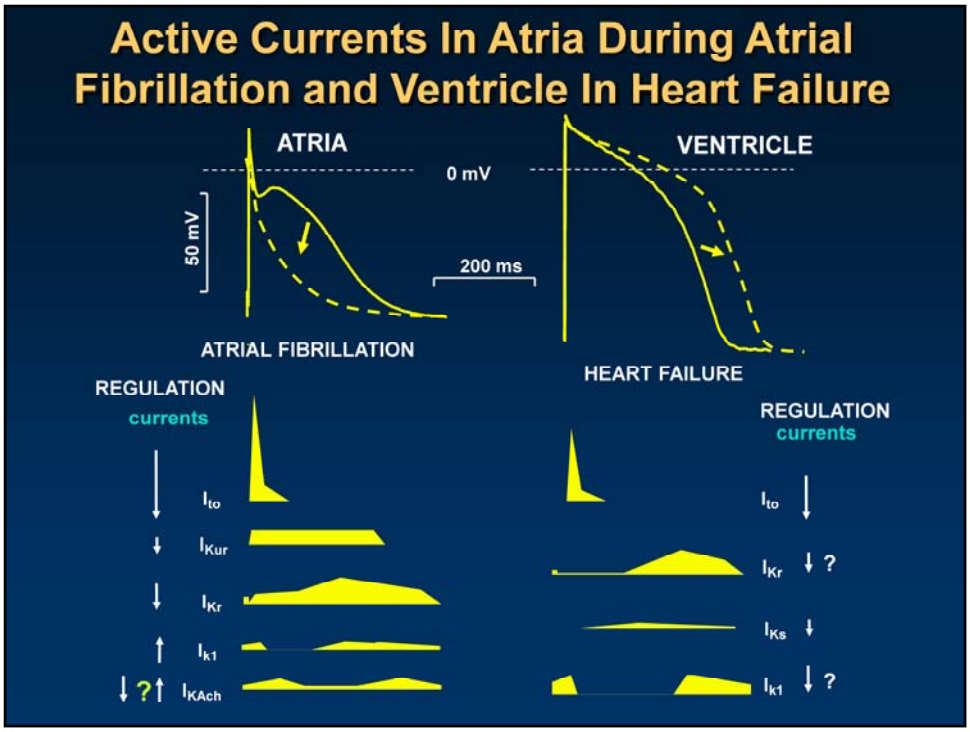
Modified from: Naccarelli & Kowey New Technologies Retreat, 2004

"Atrial Specific" Drugs
(Atrial Repolarization Delaying Agents, ARDAs)

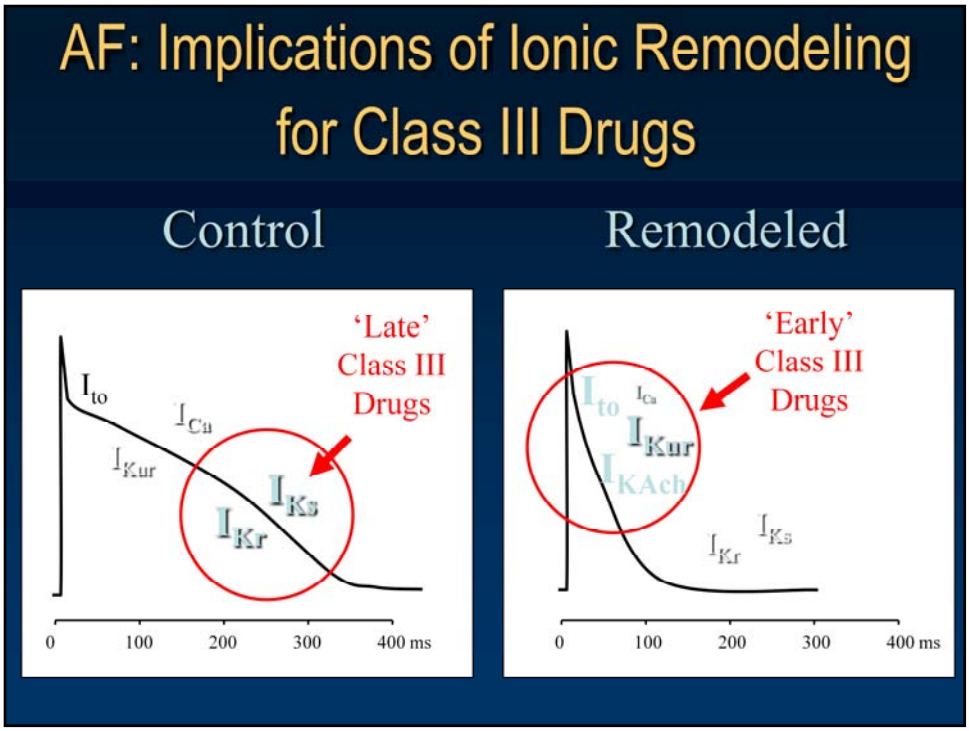
- These agents target channels that are prominent in atrial electrophysiology and play little to no role in ventricular electrophysiology.
- Many of the agents developed so far act upon more than one atrial channel; the most common being I_{Kur}.
- In at least some species, there are differences in channel expression in the right vs left atria *;
  this may allow drug effects to be relatively "atrium-specific."
- The atrial channel properties may change with remodeling, such that drug effects may be different in sinus rhythm than in the fibrillating atria.
- The clinical focus of these agents (IV, oral) may be pharmacologic cardioversion, AF prevention, or both.

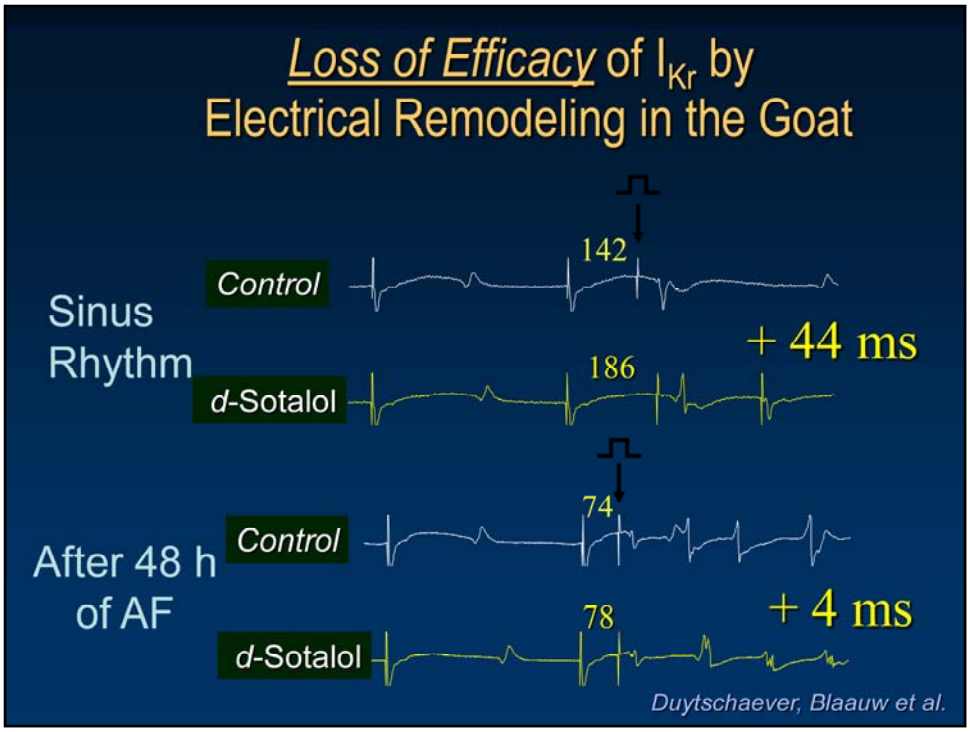
* LA APD is shorter than RA APD in at least dogs and pigs.
Li et al. Circ Res 2001; 88:1168-71.

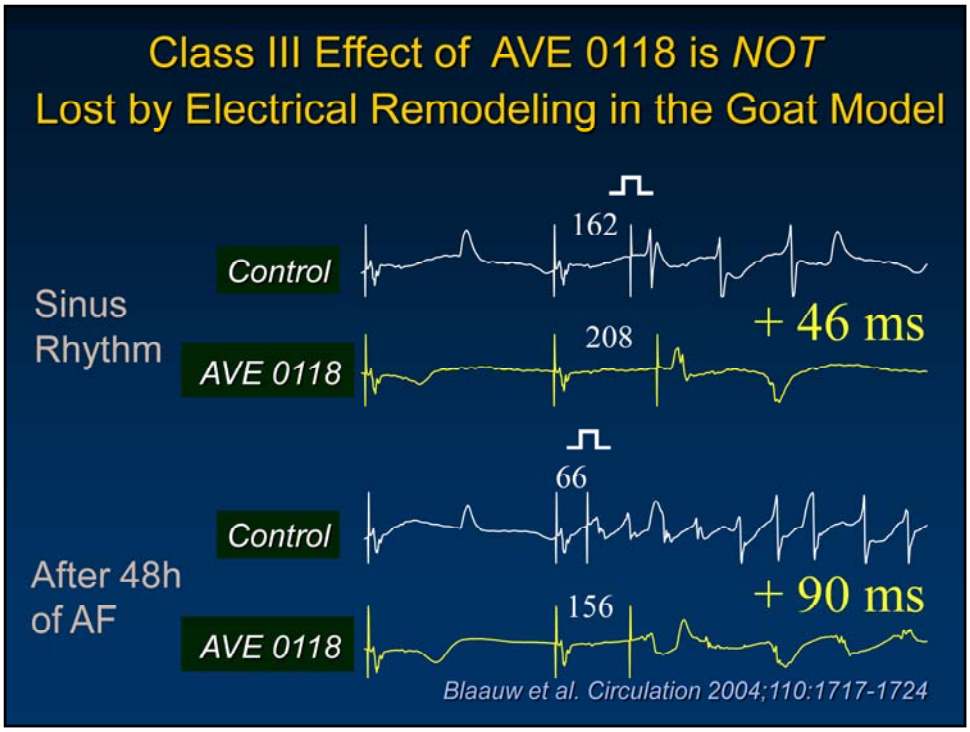

Active Currents In Atria and Ventricle
ATRIA
VENTRICLE
0 mV
50 mV
200 ms
currents
channel proteins
currents
Kv4.3+Kv1.4
KChIP2
Kv1.5 (Kv3.1)
Not expressed
(H)ERG+miRP1
KvLQT1+minK
Kir 2.1 (Kir2.x)
GIRK4
Not expressed
Kir6.2+SUR2A
SicilianGambit

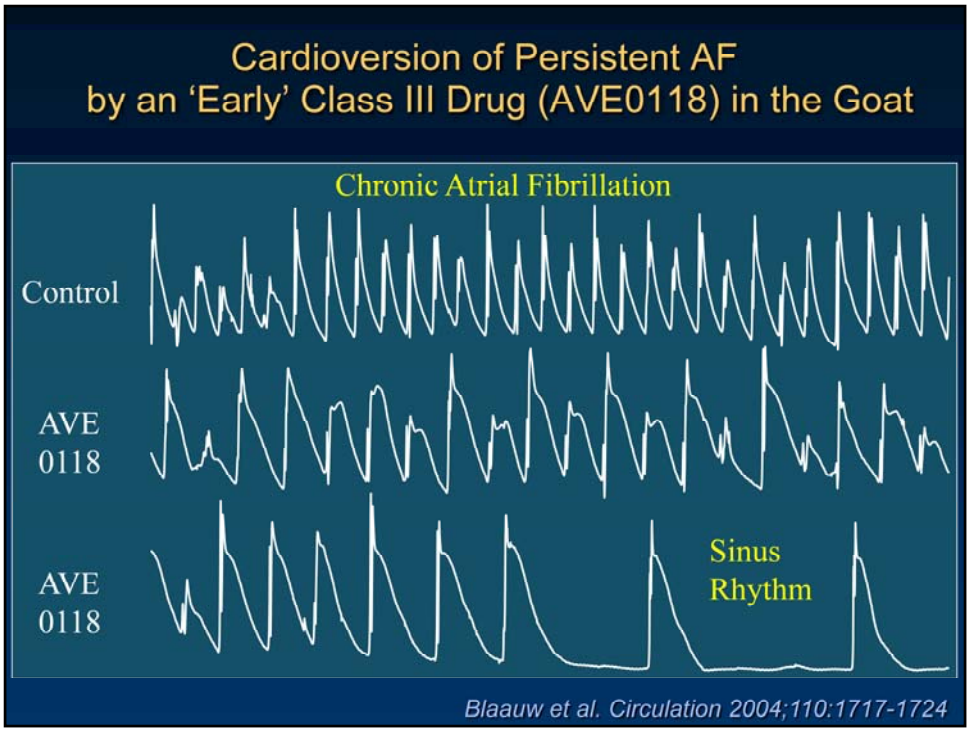

Active Currents In Atria During Atrial Fibrillation and Ventricle In Heart Failure
ATRIA
VENTRICLE
0 mV
50 mV
200 ms
ATRIAL FIBRILLATION
HEART FAILURE
REGULATION
currents
REGULATION
currents
I_{to}
I_{Kur}
I_{Kr}
I_{k1}
I_{KAch}
I_{to}
I_{Kr} ?
I_{Ks}
I_{k1} ?

AF: Implications of Ionic Remodeling for Class III Drugs

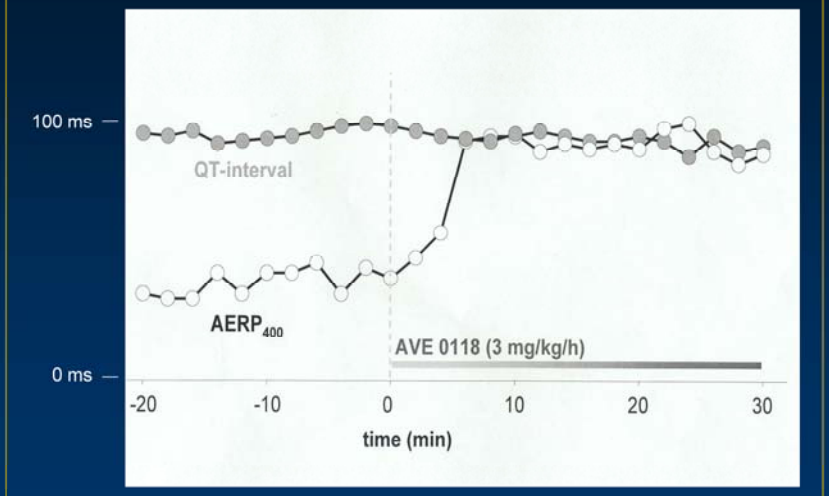



Loss of Efficacy of I_{Kr} by
Electrical Remodeling in the Goat
Sinus Rhythm
Control
142
d-Sotalol
186
+ 44 ms
After 48 h of AF
Control
74
d-Sotalol
78
+ 4 ms
Duytschaever, Blaauw et al.

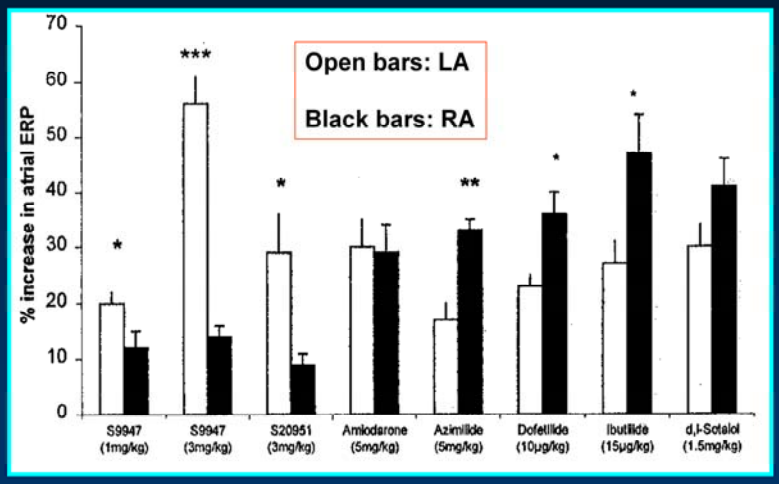

Class III Effect of AVE 0118 is NOT
Lost by Electrical Remodeling in the Goat Model
Sinus Rhythm
Control
162
AVE 0118
208
+ 46 ms
After 48h of AF
Control
66
AVE 0118
156
+ 90 ms
Blaauw et al. Circulation 2004;110:1717-1724


Cardioversion of Persistent AF
by an 'Early' Class III Drug (AVE0118) in the Goat
Chronic Atrial Fibrillation
Control
AVE
0118
AVE
0118
Sinus
Rhythm
Blaauw et al. Circulation 2004;110:1717-1724

Atrial Selectivity of AVE0118



Electrophysiological and Antiarrhythmic Effects of Novel I_{Kur} Channel Blockers S9947 and S20951 on Left vs Right Pig Atrium In Vivo in Comparison With I_{Kr} Blockers Dofetilide, Azimilide, d,l-Sotalol, and Ibutilide



Knobloch K. *Naunyn Schmiedebergs Arch Pharmacol.* 2002;366:482. Knobloch et al. Medical Science Monitor. 2004; 10:BR221-8

Vernakalant (RSD1235): The Furthest Along

[Kynapid]

Vernakalant (RSD1235): The Furthest Along [Kynapid]

Intravenous RSD1235 Selectively Prolongs the Atrial Refractory Period in Humans

		AERP600, ms	AERP400, ms	AERP300, ms	VERP600, ms	VERP400, ms
Dose 1 (n=10)	Baseline	206 ±32	188 ±31	180 ±31	251 ±19	224 ±20
	RSD1235	220 ±32*	195 ±24	181 ±16	248 ±22	227 ±16
Dose 2 (n=9)	Baseline	203 ±31	182 ±31	172 ±25	257 ±14	223 ±15
	RSD1235	228 ±23*	207 ±26*	193 ±20*	262 ±16	228 ±16

AERP=atrial effective refractory period, VERP=ventricular effective refractory period,

*P< 05 compared with baseline.

RSD – 1235: CRAFT (phase 2) RESULTS

Intravenous	Termination < 30 min	(% Termination)
Placebo	1/18 (median time 162 min)	(5.6%)
0.5+1 mg/kg	2/18	(11.1%)
2 mg/kg	8/18	(44.4%)
2+3 mg/kg	11/18 (median time 14 min)	(61.1%)* *p<.0005

Roy et al. J Am Coll Cardiol 2004;44:2355-2361

Vernakalant: Important Studies to Date with the IV Formulation

- **Act 1:** Pivotal, double-blind, placebo-controlled, phase 3 trial of 416 pts with AF *.
- **Act 3:** Pivotal, double-blind, placebo-controlled, phase 3 trial of 276 pts with AF ***
- **Act 2:** A post-op AF study **
- **Results were similar in each:**
  - Conversion of recent-onset AF (3hr-7d): 52% vs 4% ($p<0.001$) [median time 8-11 min]
  - Conversion of all AF (3 hr-45 d): 38-41% vs 3-4% ($p<0.001$)
  - Ineffective for conversion of A. Flutter
  - Potentially serious AEs: 1.4-2% vs 0-1% (over 30 days); no TdP

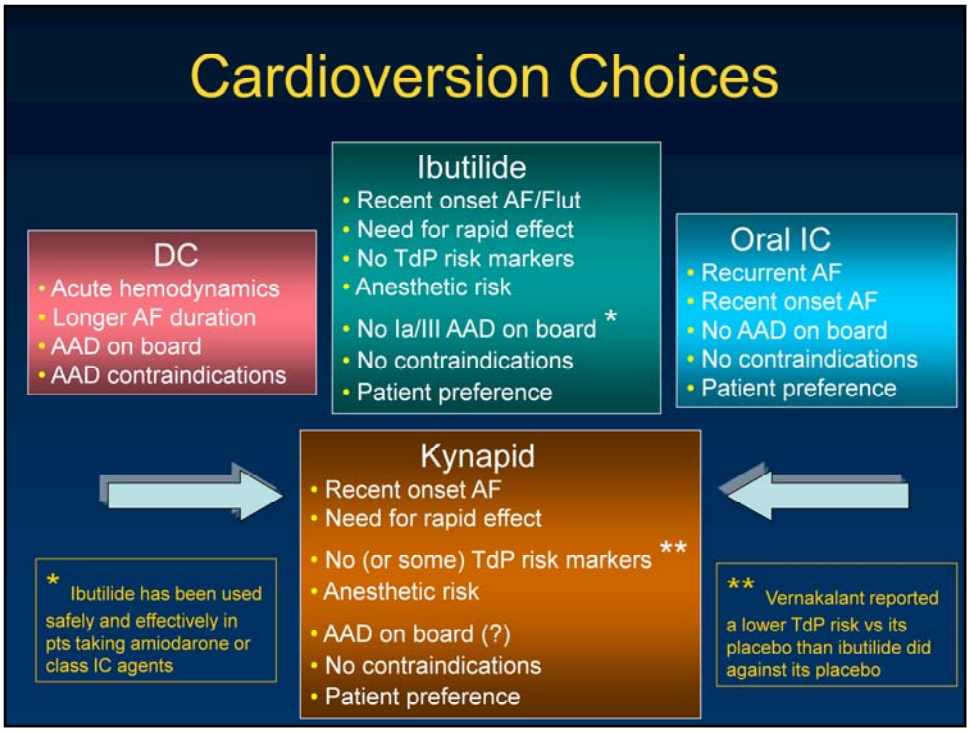
* Roy D. Heart Rhythm Society; April 22-24, 2004; New Orleans, Louisiana

** Kowey P. et al , presented at AHA Annual Scientific Sessions, Orlando, Nov 6, 2007 *** Pratt et al JACC 2006;47:804

Vernakalant (RSD1235): The Furthest Along

- Most common AEs: sneezing, dysgeusia, paraesthesias – related to time of Cmax (7-15 min)
- Rare significant adverse hemodynamic effects: bradycardia (1.7%), hypotension (usually <10 mm/hg, 1.3%)*
- There were 2 VFs in the clinical trials: (1 death in a severe AS pt) suggesting a rate of 1.4 per 1000 pts with previous risk factors. * **
- Extremely rare TdP (1 in a protocol violator, after ibutilide)
- Trials excluded severe heart failure and acute MI.
  - The PI is expected to exclude symptomatic or a history of CHF, acute coronary syndrome, and hypotension.

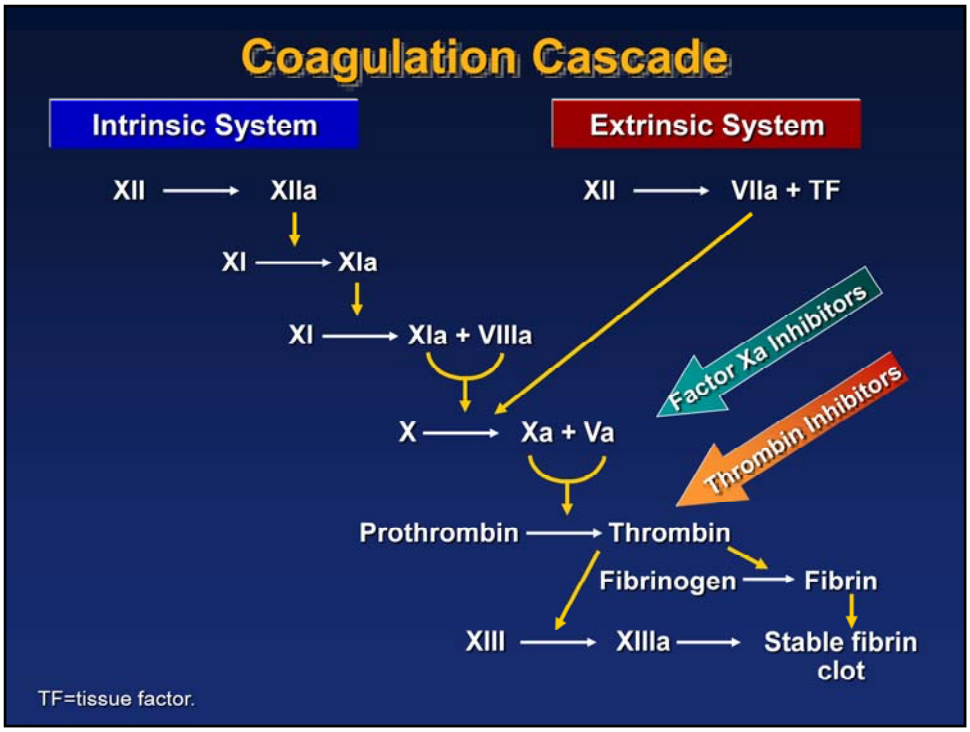
* *Data on File at Astellas Pharma* ** *www.bloomberg.com 12/12/07*


Cardioversion Choices
Ibutilide
• Recent onset AF/Flut
• Need for rapid effect
• No TdP risk markers
• Anesthetic risk
• No Ia/III AAD on board *
• No contraindications
• Patient preference
DC
• Acute hemodynamics
• Longer AF duration
• AAD on board
• AAD contraindications
Oral IC
• Recurrent AF
• Recent onset AF
• No AAD on board
• No contraindications
• Patient preference
Kynapid
• Recent onset AF
• Need for rapid effect
• No (or some) TdP risk markers **
• Anesthetic risk
• AAD on board (?)
• No contraindications
• Patient preference
* Ibutilide has been used safely and effectively in pts taking amiodarone or class IC agents
** Vernakalant reported a lower TdP risk vs its placebo than ibutilide did against its placebo

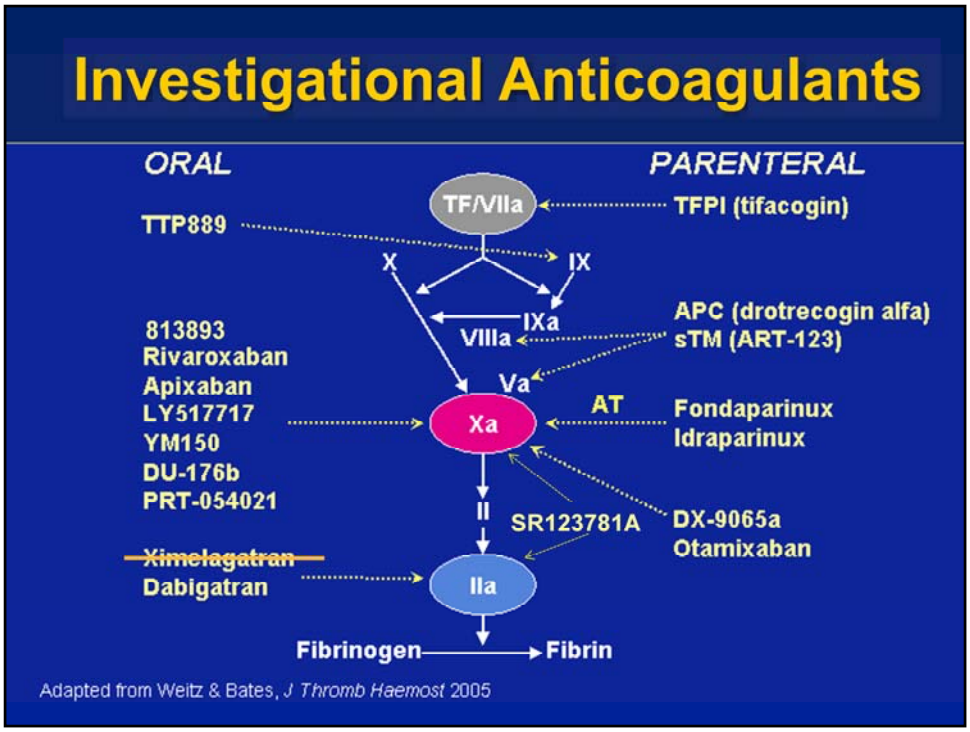
Anticoagulation: New Horizons

- Newer platelet inhibitor approaches (alone or in combinations):
  - The ACTIVE trials (ACTIVE W terminated early)
- Alternative agents are being studied, such as parenteral factor Xa inhibitors
    - AMADEUS (IV) terminated early due to excess bleeding
    - Oral trials pending
- Oral thrombin inhibitors and factor Xa inhibitors: the real wave of the future?
  - Ximelagatran
    - Withdrawn due to hepatic AEs
  - Other DTIs under study: dabigatran and others
  - Factor Xa inhibitors under study: rivaroxaban, apixaban, and others
- Catheter-delivered left atrial appendage occluders
- Thoracoscopic left atrial appendage occlusion*

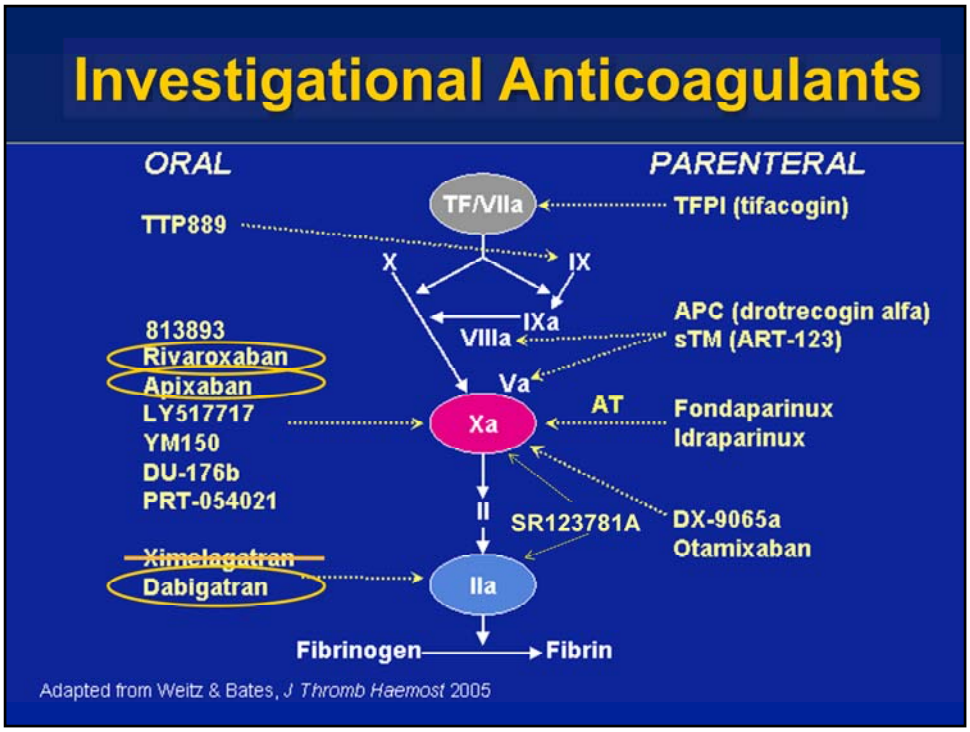
*Blackshear et al. *J Am Coll Cardiol*. 2003;42:1249.


Coagulation Cascade
Intrinsic System
Extrinsic System
XII
XIIa
XI
XIa
IX
XIa + VIIIa
XII
VIIa + TF
X
Xa + Va
Factor Xa Inhibitors
Thrombin Inhibitors
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIII
XIIIa
Stable fibrin clot
TF=tissue factor.

Investigational Anticoagulants



Investigational Anticoagulants



New Oral Anticoagulants for AF

- Direct thrombin inhibitors and factor Xa inhibitors now under study appear to have the benefit of uniform dosing for AF, absence of food interactions, minimal if any drug interactions, absence of INR monitoring, and rapid kinetics such that anticoagulation begins within hours and is gone within a day of drug discontinuation.
- Rivaroxaban and dabigatran are now approved in Europe for VTE prevention post orthopedic surgery (U.S. approval for rivaroxaban is pending)
- Current AF trials at or nearing completion:
  - RELY: dabigatran (DTI) completed, data pending
  - ROCKET AF: rivaroxaban, (Xa inhibitor) due to complete in 2010
  - ARISTOTLE and AVERROES*: apixaban (Xa inhibitor), due to complete in 2010

*A smaller trial in patients who cannot take a VKA

Rivaroxaban

- Once daily dosing
- Superior to enoxaparin in preventing VTE after knee replacement surgery and THA (phase III studies– the RECORD trials) and effective in preventing DVT and PE after orthopedic surgery (phase IIb trials).
- No “liver signal” in VTE trials.
- No significant drug interactions.
- Excess bleeding in early trials with doses of 30 mg/d or higher.
- Filed for marketing for VTE in the European Union in Nov 2007.
- Being studied for stroke prevention in AF and for ACS.

Rivaroxaban: Clinical Trial Program

- >20,000 pts evaluated so far in phase II and III programs, with 50,000 ultimately expected.
- RECORD: 4 trials with different length and dosing, comparing rivaroxaban to enoxaparin for VTE prevention after hip or knee surgery.
- MAGELLAN: VTE prevention in hospitalized medical patients.
- ATLAS: a dose ranging secondary prevention trial in ACS: 3 doses, + ASA, +/- clopidogrel.
- EINSTEIN: Rx of existing DVT, PE.
- ROCKET AF: a primary prevention trial in AF.

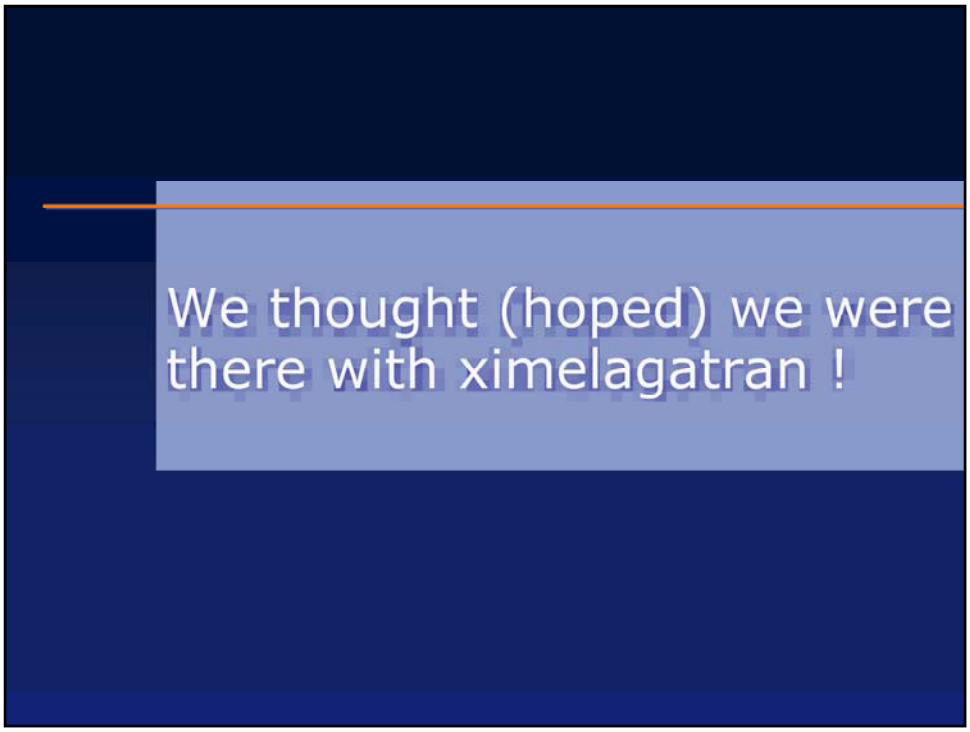
ROCKET AF

- A prospective, randomized, double-blind, double-dummy, event-driven, non-inferiority study comparing the efficacy and safety of once a day fixed-dose oral rivaroxaban with adjusted dose warfarin (INR 2-3) for the prevention of stroke and systemic embolism in subjects with non-valvular AF and prior embolism or $CHADS_2$ score of at least 3 (10% will have $CHADS_2$ score of 2).
- Primary endpoint: stroke or SE
- Excluded: planned CV, prosthetic valves, pregnancy
- Non-inferiority trial; expected warfarin event rate 2.3%
- Enrolled 12/06-6/09; anticipates ~14,000 pts with completion in mid 2010.

  [ARISTOTLE is a similar trial with apixaban, anticipating ~15, 000 pts with completion estimated for late 2010]

Direct Thrombin Inhibitors

- Ximelagatran
- Dabigatran

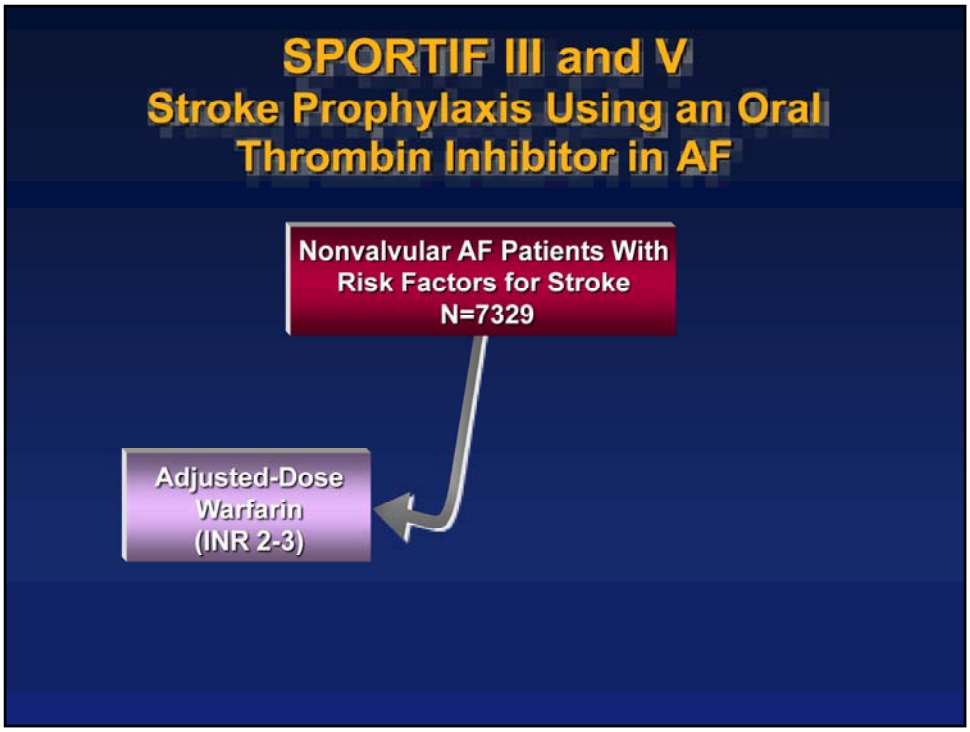

We thought (hoped) we were there with ximelagatran !

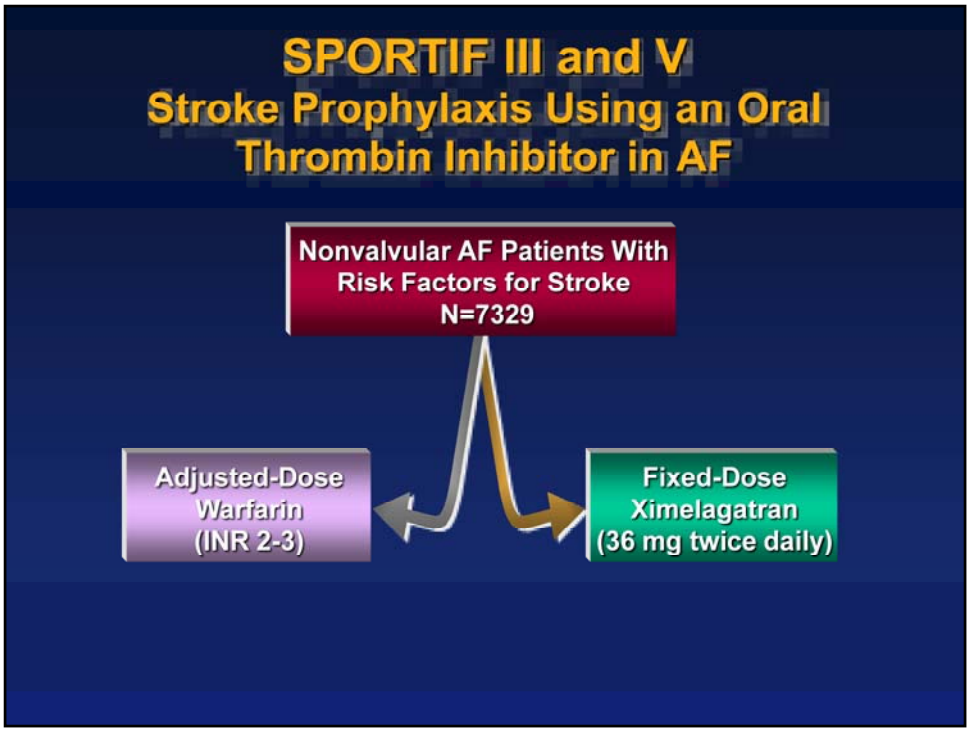
Ximelagatran (Exanta) Highlights

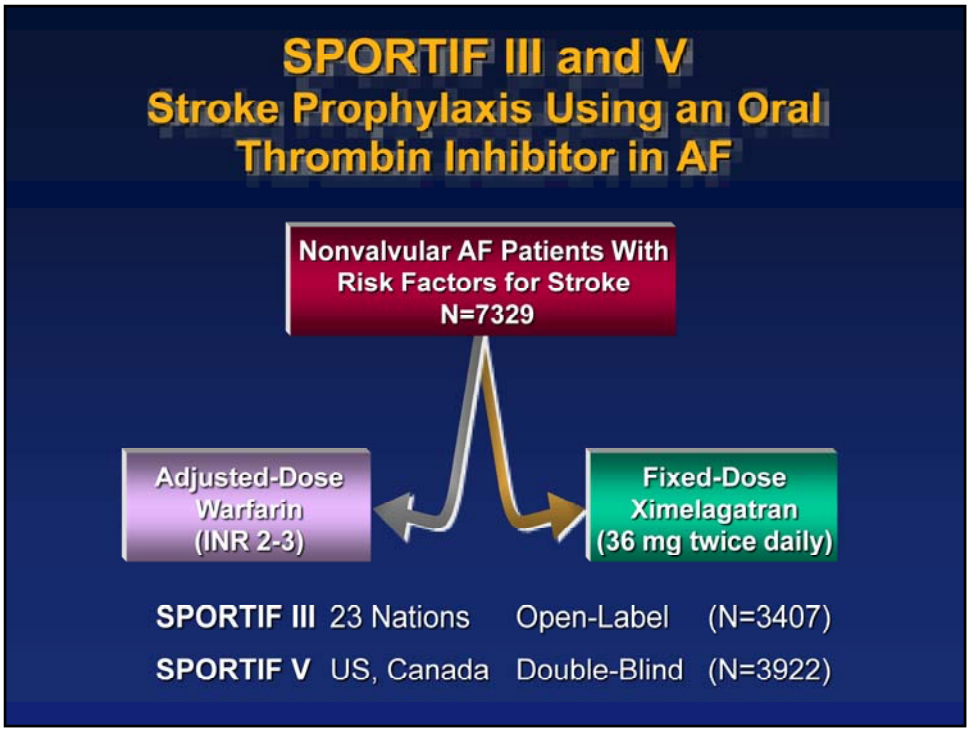
- Oral pro-drug of melagatran, a direct thrombin inhibitor.
- 2 hour onset, 5 hour half-life.
- BID dosing with a fixed dose.
- Anticoagulation onset and offset in a day.
- No food or drug interactions (except erythromycin).
- Proven non-inferior to warfarin in efficacy in DVT and AF, with a lower risk of bleeding.
- No coagulation test monitoring.
- Small incidence of reversible elevation of hepatic enzymes (with a peak incidence 60-120 days after initiation of treatment).
- Reverse effects with transfusion.

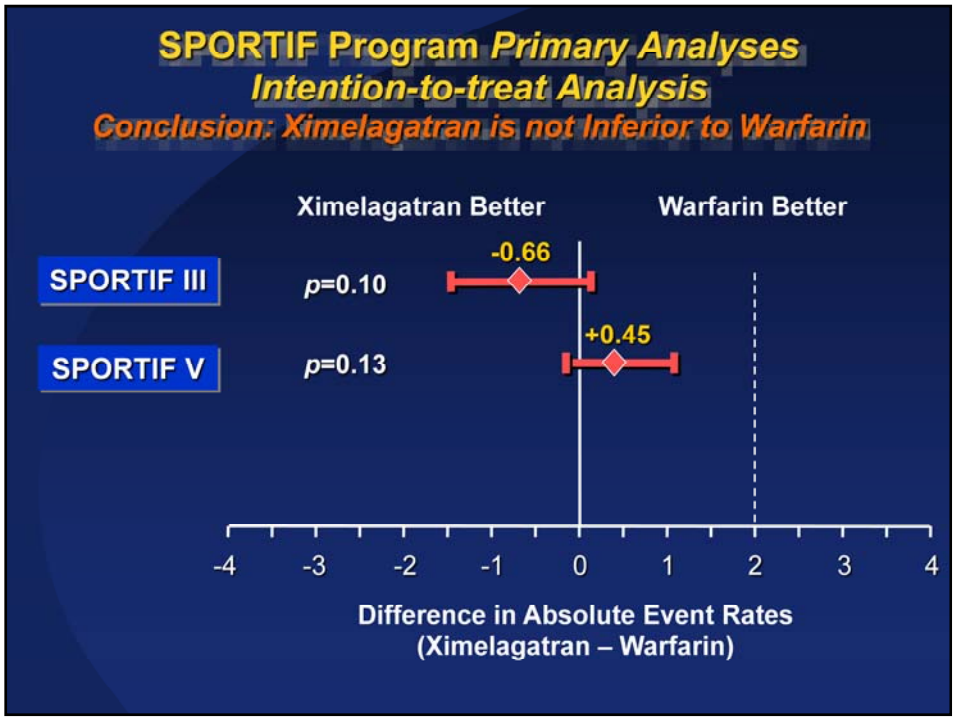
SPORTIF III and V
Stroke Prophylaxis Using an Oral Thrombin Inhibitor in AF

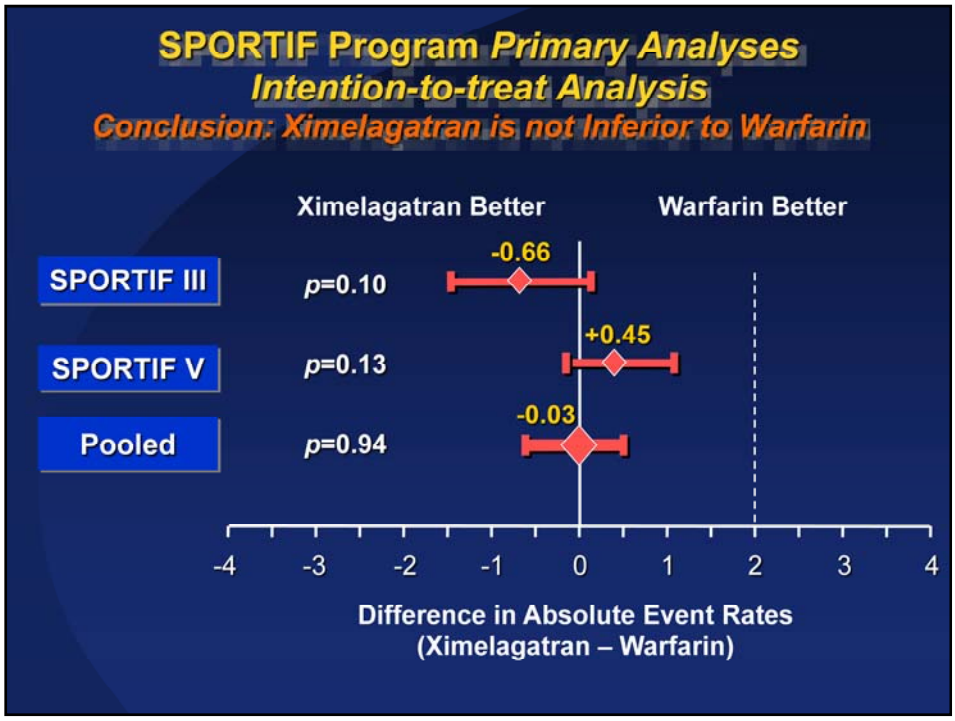
Nonvalvular AF Patients With Risk Factors for Stroke
N=7329

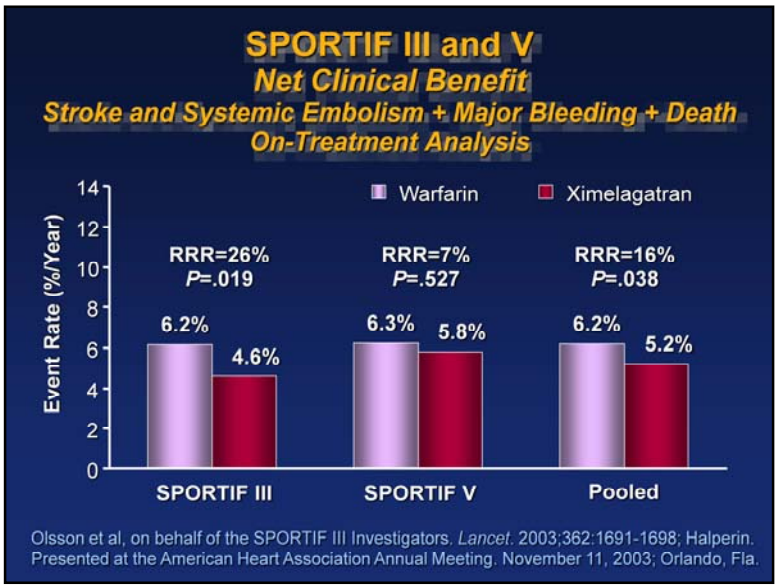

SPORTIF III and V
Stroke Prophylaxis Using an Oral Thrombin Inhibitor in AF
Nonvalvular AF Patients With Risk Factors for Stroke N=7329
Adjusted-Dose Warfarin (INR 2-3)


SPORTIF III and V
Stroke Prophylaxis Using an Oral Thrombin Inhibitor in AF
Nonvalvular AF Patients With Risk Factors for Stroke N=7329
Adjusted-Dose Warfarin (INR 2-3)
Fixed-Dose Ximelagatran (36 mg twice daily)


SPORTIF III and V
Stroke Prophylaxis Using an Oral Thrombin Inhibitor in AF
Nonvalvular AF Patients With Risk Factors for Stroke N=7329
Adjusted-Dose Warfarin (INR 2-3)
Fixed-Dose Ximelagatran (36 mg twice daily)
SPORTIF III 23 Nations Open-Label (N=3407)
SPORTIF V US, Canada Double-Blind (N=3922)


SPORTIF Program Primary Analyses
Intention-to-treat Analysis
Conclusion: Ximelagatran is not Inferior to Warfarin
Ximelagatran Better
Warfarin Better
SPORTIF III
p=0.10
-0.66
SPORTIF V
p=0.13
+0.45
-4
-3
-2
-1
0
1
2
3
4
Difference in Absolute Event Rates
(Ximelagatran – Warfarin)

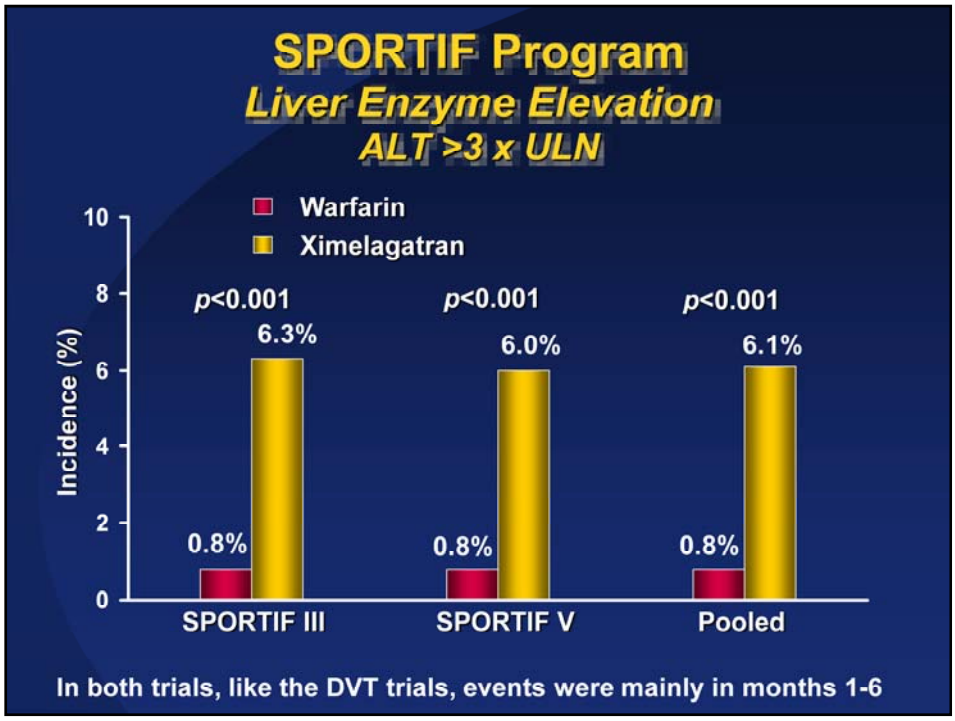

SPORTIF Program Primary Analyses
Intention-to-treat Analysis
Conclusion: Ximelagatran is not Inferior to Warfarin
Ximelagatran Better
Warfarin Better
SPORTIF III
p=0.10
-0.66
SPORTIF V
p=0.13
+0.45
Pooled
p=0.94
-0.03
-4
-3
-2
-1
0
1
2
3
4
Difference in Absolute Event Rates
(Ximelagatran – Warfarin)

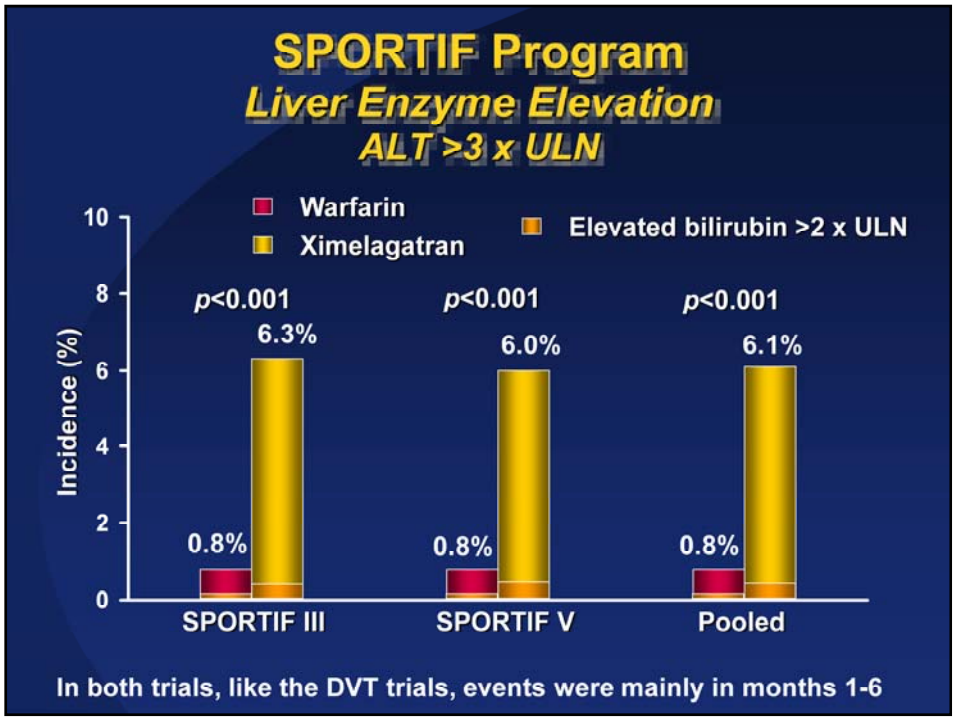


The on-treatment analysis of net clinical benefit (stroke and systemic embolism plus major bleeding and death) revealed a significant reduction in events in the SPORTIF III and predefined pooled analysis, but the reduction was not significant in the SPORTIF V trial. Patients on warfarin had consistently higher events, with 6.2% in SPORTIF III; 6.3% in SPORTIF V; and 6.2% when the 2 studies were combined. Of patients on ximelagatran, 4.6% had primary events, major bleeding, or death in SPORTIF III; 5.8% in SPORTIF V; and 5.2% in the pooled data. This indicates a favorable overall risk:benefit ratio for ximelagatran.

Olsson SB et al, on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691-1698.

Halperin JL. Stroke prevention using the direct oral thrombin inhibitor ximelagatran in patients with nonvalvular atrial fibrillation: SPORTIF V. Presented at the American Heart Association Annual Meeting. November 11, 2003; Orlando, Fla.


SPORTIF Program
Liver Enzyme Elevation
ALT >3 x ULN
Warfarin
Ximelagatran
Incidence (%)
10
8
6
4
2
0
p<0.001
p<0.001
p<0.001
6.3%
6.0%
6.1%
0.8%
0.8%
0.8%
SPORTIF III
SPORTIF V
Pooled
In both trials, like the DVT trials, events were mainly in months 1-6


SPORTIF Program
Liver Enzyme Elevation
ALT >3 x ULN
Warfarin
Ximelagatran
Elevated bilirubin >2 x ULN
Incidence (%)
10
8
6
4
2
0
p<0.001
6.3%
0.8%
p<0.001
6.0%
0.8%
p<0.001
6.1%
0.8%
SPORTIF III
SPORTIF V
Pooled
In both trials, like the DVT trials, events were mainly in months 1-6

SPORTIF Conclusions

In high-risk patients with nonvalvular AF, ximelagatran offers:

- Fixed oral dosing without coagulation monitoring
- Effectiveness noninferior to well controlled warfarin in preventing stroke and systemic embolic events
- Less bleeding than warfarin
- The potential for an increase in ALT levels in ~6% of patients
- A promising treatment option for prevention of thromboembolism

Ximelagatran – Sept 2004

- The data concerning ximelagatran was presented to the FDA advisory panels in Sept 2004.
- The drug was not approved by the panels despite its huge potential to reduce the adverse outcomes associated with underuse of warfarin.
  - Hepatic toxicity (with rare deaths)
  - Concerns about the validity of the statistical design used in the trial
- Other oral thrombin inhibitors are under development.

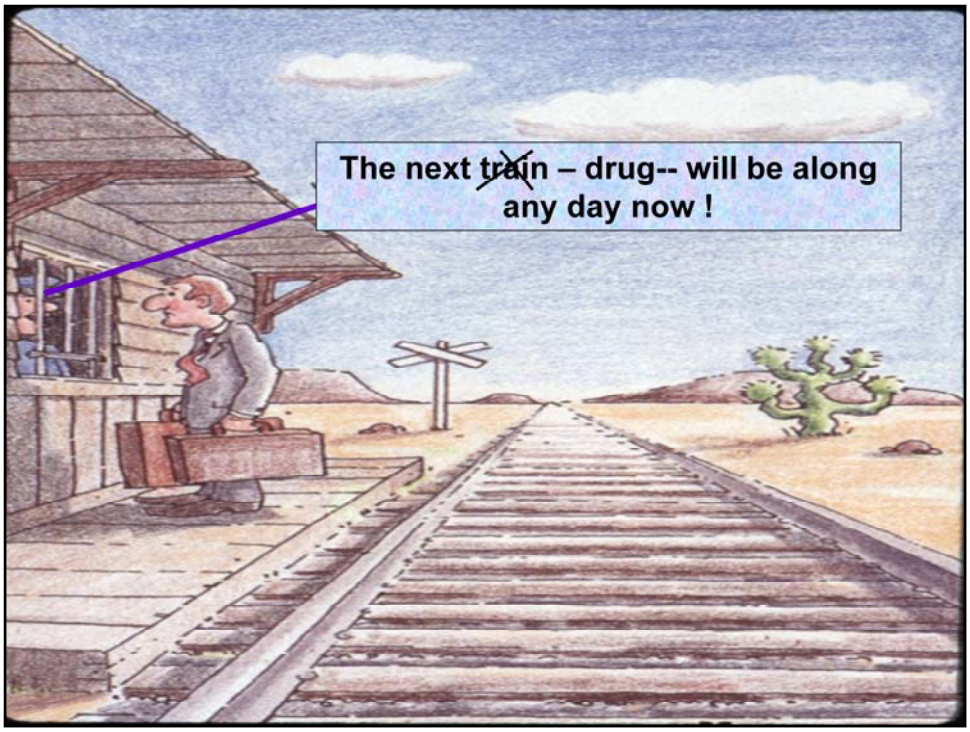
Dabigatran

- Onset of action <1 hr; T ½ 12-15 hrs.
- Increases aPTT, PT, TT, ECT but these are not used to monitor therapy. ECT and TT are sensitive to dabigatran effect.
- No food interaction.
- Hepatic enzyme elevations substantially less (<1-2%) than with ximelagatran
- It's A. Fib trial, RELY, has just recently been completed (March 2009)
  - Data analysis is underway
  - Presentation of results will occur later this year

The RELY Trial

- A phase III efficacy and safety trial of 150 mg bid, 300 mg bid, vs open-label warfarin in a prospective, randomized, dabigatran-dose blinded parallel-armed trial in non-valvular AF for the prevention of stroke and SEE initially targeting 15,000 pts.
  - This followed the successful phase II trial in AF: PETRO
- Enrollment was completed in 2007 and the minimum 1 yr follow-up was completed in March 2009.
- Data presentation is anticipated for the ESC meetings 2009


LOOKOUT AHEAD
LOOKOUT!
Hopefully, RELY, ROCKET AF will not end like SPORTIF


The next train – drug-- will be along any day now !