# Atrial Fibrillation
# Current Concepts and Advances in Management

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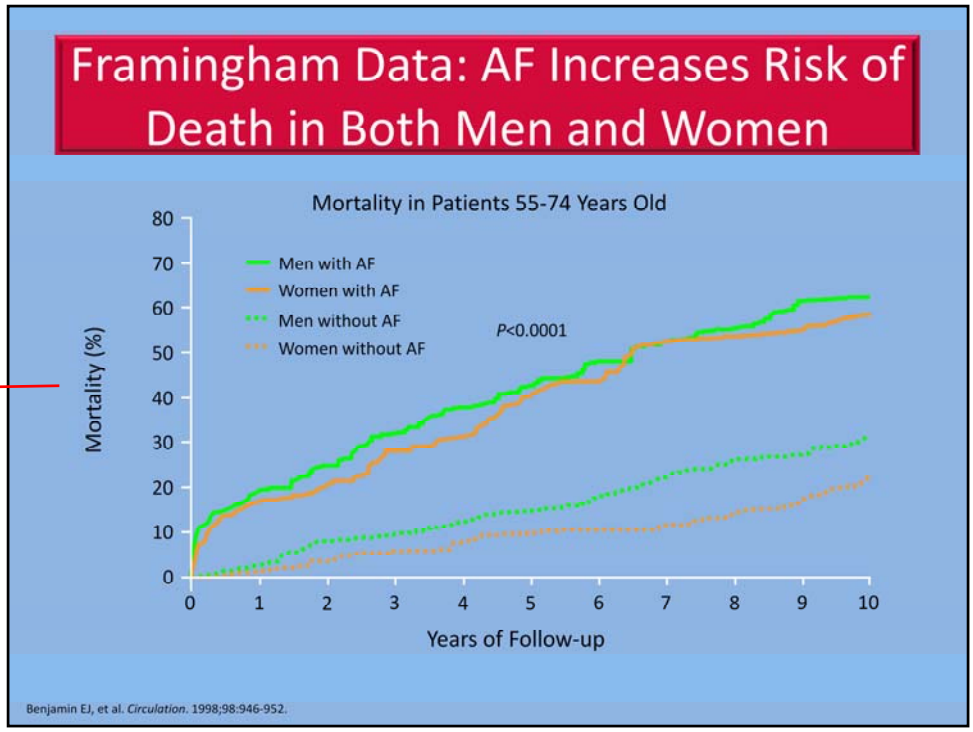
# Disclosures

- Consultant &/or Investigator
  - Medtronic, St. Jude, Sanofi-Aventis, NHLBI
- Other disclosures
  - Editor, Elsevier, Springer, Cardiotext

Benjamin/Circ May 2008/p948/Fig A

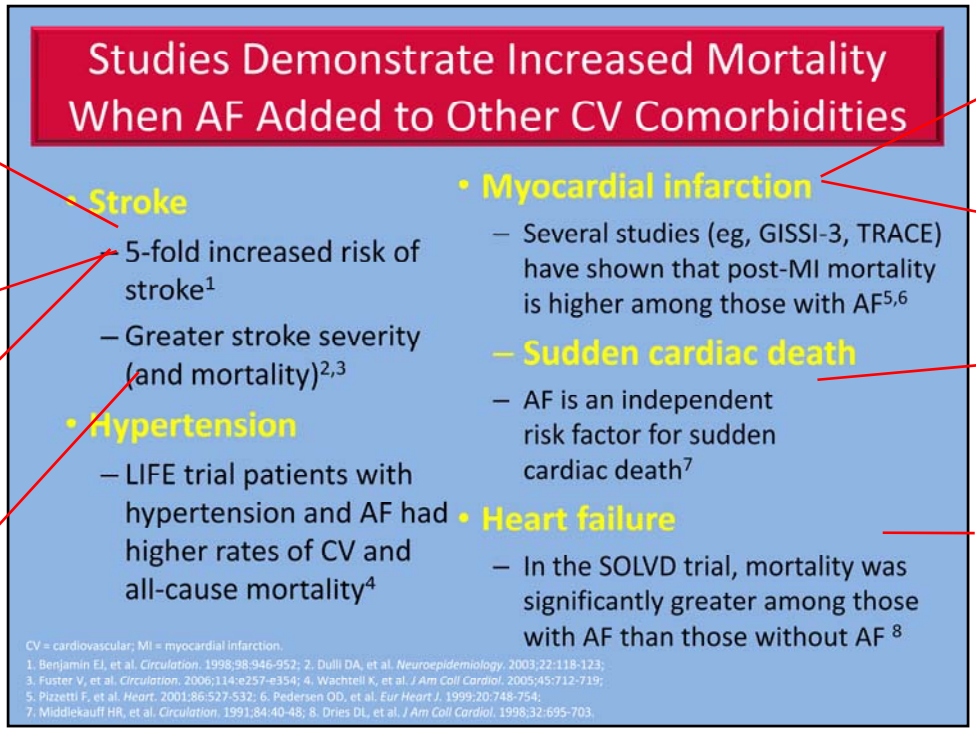



As shown here, data from the Framingham Heart Study have helped to establish an association between atrial fibrillation and excess mortality that is **independent of** associated cardiac conditions and risk factors in both men and women. **(Benjamin/Circ May 2008/p950/col2/lines 1-9)**

This study examined mortality among patients aged 55 to 94 years who developed atrial fibrillation during the 40-year follow-up period of the original Framingham study. A total of 296 men and 325 women developed atrial fibrillation and met eligibility criteria. After adjustment for risk factors including age, hypertension, smoking, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke/transient ischemic attack, atrial fibrillation was found to be associated with a 1.5- to greater than 1.9-fold mortality risk. **(Benjamin/Circ May 2008/p946, lines A4-A9 and p950/col2/lines 1-9)**

This slide shows mortality for patients aged 55 to 74 years.

Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-952.




Benjamin. Circulation.Sept. 1998/p946/C1 lines 14-15

Dulli. Neuroepidemiology. March.2003/p118/ c1/lines A16-A20

Fuster. Circulation. August.2006/ pe267/c1/ lines 30-32

Wachtell. JACC.March. 2005/p717/ Table 3

Pedersen. Eur Heart J. May.1999/p748/c2/ lines A30—A33 and lines A41-45

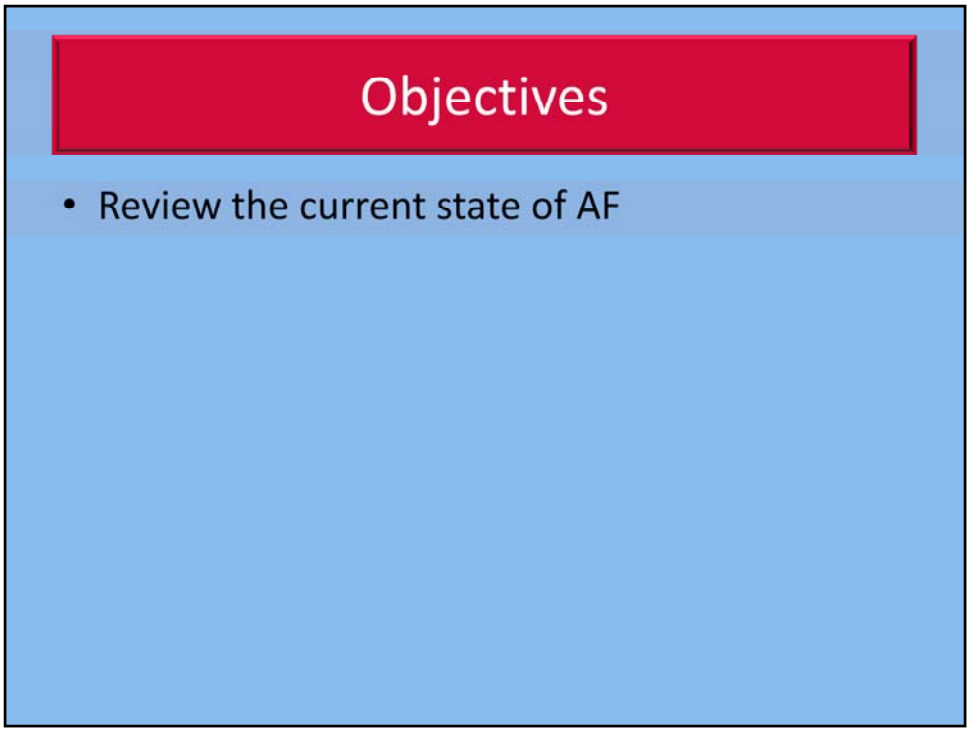
Pizzetti.Heart.July. 2001/p527/ lines A17-A22

Middlekauff. Circulation.July.1991/ p44/c1/lines 13-16 & c2/lines 14-15

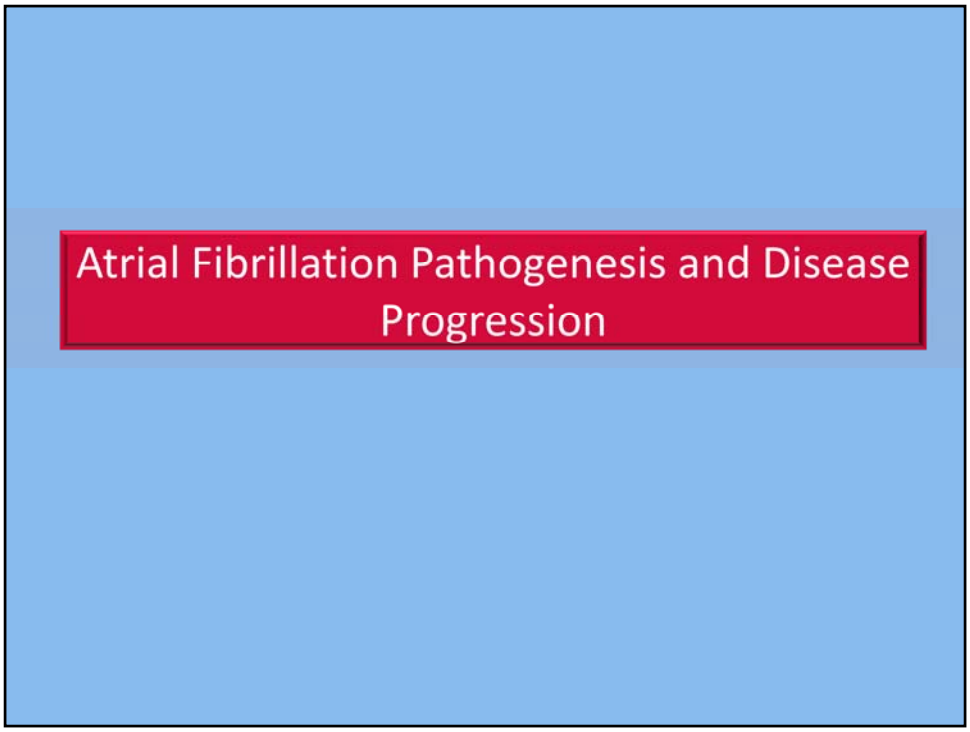
Dries.Sept.1998/ p695/c2/lines A12-A15

Several studies have documented the relationship between atrial fibrillation and other types of cardiovascular disease.
As noted by Krahn and associates, the presence of atrial fibrillation with comorbid conditions such as myocardial infarction, hypertension, and heart failure have been shown to increase mortality. Moreover, cardiovascular diseases such as hypertension and ischemic heart disease often precede atrial fibrillation and are independently associated with an increased incidence of atrial fibrillation.[1] **(Krahn.Am J Med. May.1995/p476/c2/lines 1-15)**
Therefore, atrial fibrillation in the presence of underlying cardiovascular disease is among the strongest predictors of worsening disease and mortality.[2] **(Fuster.Circulation.August.2006/pe267/c1/lines 1-6)** Furthermore, atrial fibrillation is a strong independent predictor of stroke and hospitalization.[3] **(Stewart.Am J Med.October.2002/p359/c2/lines A1-A8)**

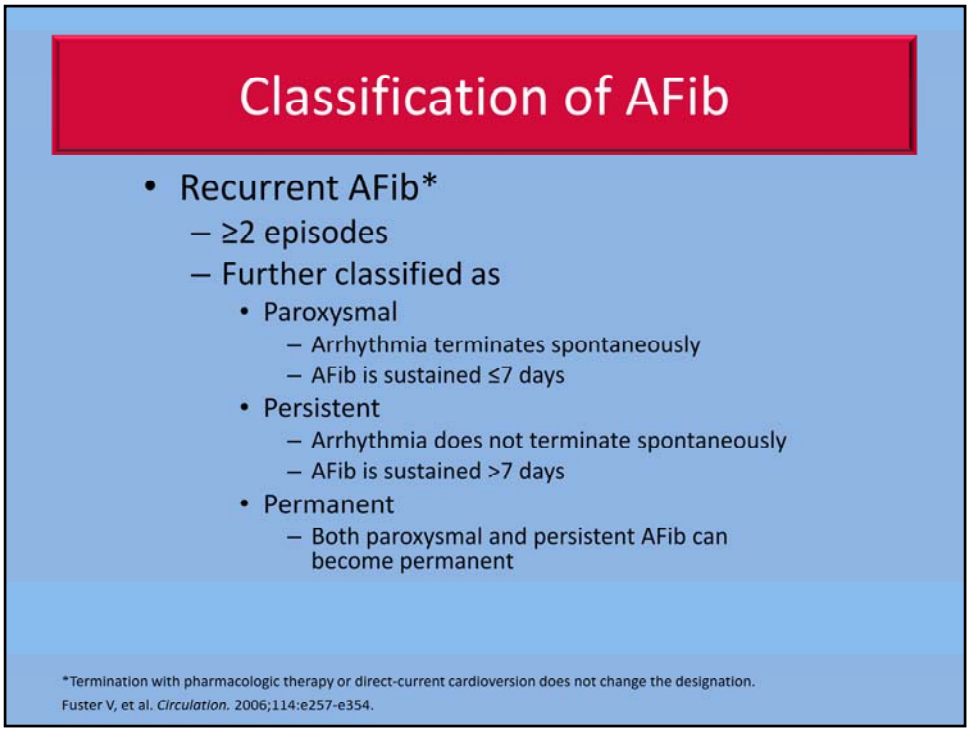

1. Krahn AD, Manfreda J, Tate RB, Mathewson AL, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med.* 1995;98:476-484.
2. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients 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 (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation.* 2006;114:e257-e354.
3. Stewart S, Hart CL, Hole DJ, McMurray AD. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med.* 2002;113:359-364.




The objectives for this presentation are as follows:
To review the current state of atrial fibrillation
To present clinical data on MULTAQ and to understand the inappropriate and appropriate patient selection for treatment with MULTAQ



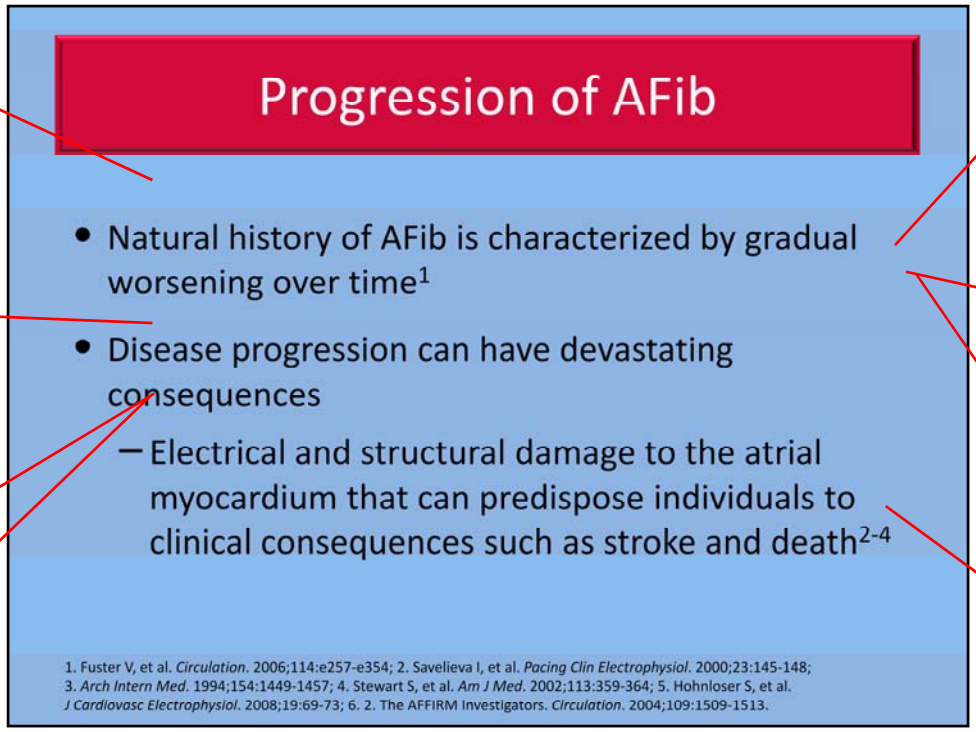
Fuster.Circulation. August.2006/ p265/c1/ lines 17-22




Recent guidelines recommend a classification system based on the temporal pattern of the arrhythmia. When a patient has 2 or more episodes, AFib is considered ***recurrent***. If AFib terminates spontaneously, it is classified as ***paroxysmal***. If AFib is sustained for more than 7 days, it is classified as ***persistent***. Termination with pharmacologic therapy or direct-current cardioversion does not change the designation. **(Fuster.Circulation.August.2006/pe265/c1/lines 17-22)**

These categories are not mutually exclusive in a particular patient, who may have several episodes of paroxysmal AFib and occasional persistent AFib, or the reverse. **(Fuster.Circulation.August.2006/pe265/c1/lines 27-29)**

Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 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 (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.




Fuster. Circulation. August.2006 /pe265/c1/ lines 17-22 and pe286/c2/line 52

Fuster. Circulation. August. 2006/pe265/ c1/lines 17-22

Hohnloser. J Cardiovasc Electrophysiol. 2007/p4/c1/ lines 22-30

Fuster. Circulation. August. 2006/pe268/ c2/lines 13-15

Savelieva. Pacing Clin Electrophysiol. February.2000/ p146/c2/ lines 9-12

Arch Intern Med. July.1994/p1449/ c1/ lines 1-2

Stewart.Am J Med. October.2002/ p359/c2/ lines A13-A15

AFFIRM Investigators. Circulation. March.2004/ p1513/c1/ lines 45-47

Atrial fibrillation is a progressive disease that worsens over time.[1]
**(Fuster.Circulation.August.2006/pe265/c1/lines 17-22 andpe286/c2/line 52)**

As aforementioned, the progressive nature of AFib can result in a worsening of cardiac remodeling. This may ultimately result in increased morbidity and mortality.[2-4]
**(Savelieva. Pacing Clin Electrophysiol.February.2000/p146/c2/lines 9-12; Arch Intern Med.July.1994/p1449/c1/ lines 1-2; Stewart.Am J Med.October.2002/p359/c2/lines A13-A15)**

Therefore, treatment of AFib may be an effective way to halt the progression of the disease.[1,5] **(Hohnloser.J Cardiovasc Electrophysiol.2007/p4/c1/lines 22-30; Fuster. Circulation.August.2006/pe268/c2/lines 13-15)**

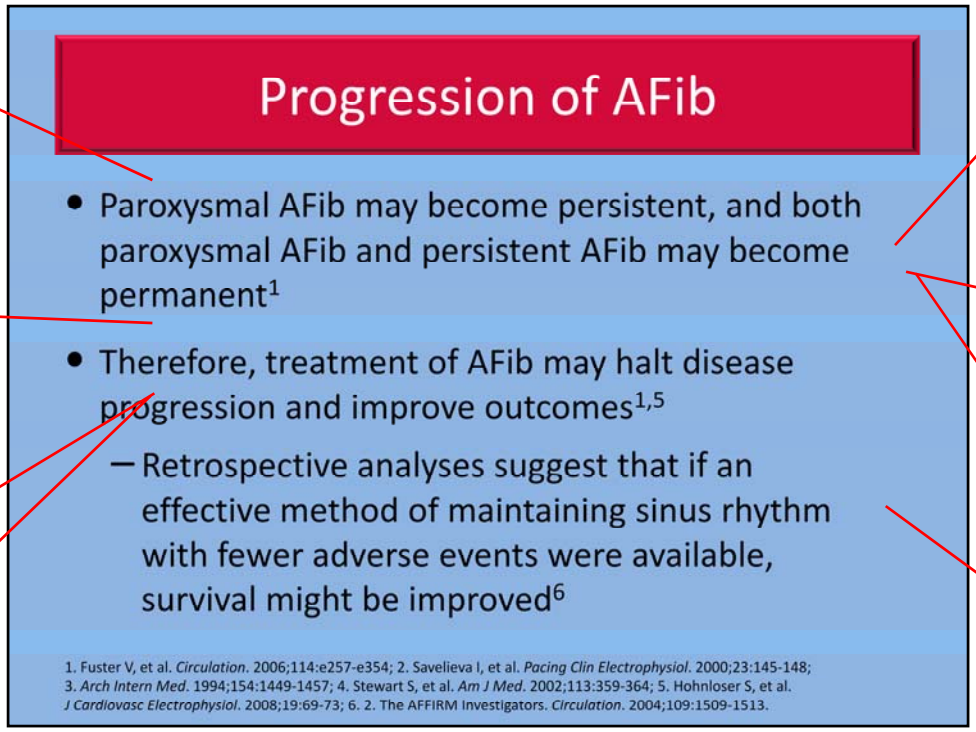

1. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.
2. Savelieva I, Camm AJ. Silent atrial fibrillation—another Pandora's box. *Pacing Clin Electrophysiol*. 2000;23:145-148.
3. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449-1457.
4. Stewart S, Hart CL, Hole DJ, McMurray JJ.A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359-364.
5. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. *J Cardiovasc Electrophysiol*. 2008;19:69-73.

Fuster. Circulation. August.2006 /pe265/c1/ lines 17-22 and pe286/c2/line 52

Fuster. Circulation. August. 2006/pe265/ c1/lines 17-22

Hohnloser. J Cardiovasc Electrophysiol. 2007/p4/c1/ lines 22-30

Fuster. Circulation. August. 2006/pe268/ c2/lines 13-15




Savelieva. Pacing Clin Electrophysiol. February.2000/ p146/c2/ lines 9-12

Arch Intern Med. July.1994/p1449/ c1/ lines 1-2

Stewart.Am J Med. October.2002/ p359/c2/ lines A13-A15

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Therefore, treatment of AFib may be an effective way to halt the progression of the disease.[1,5] **(Hohnloser.J Cardiovasc Electrophysiol.2007/p4/c1/lines 22-30; Fuster. Circulation.August.2006/pe268/c2/lines 13-15)**


1. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 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 (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.
2. Savelieva I, Camm AJ. Silent atrial fibrillation—another Pandora's box. *Pacing Clin Electrophysiol*. 2000;23:145-148.
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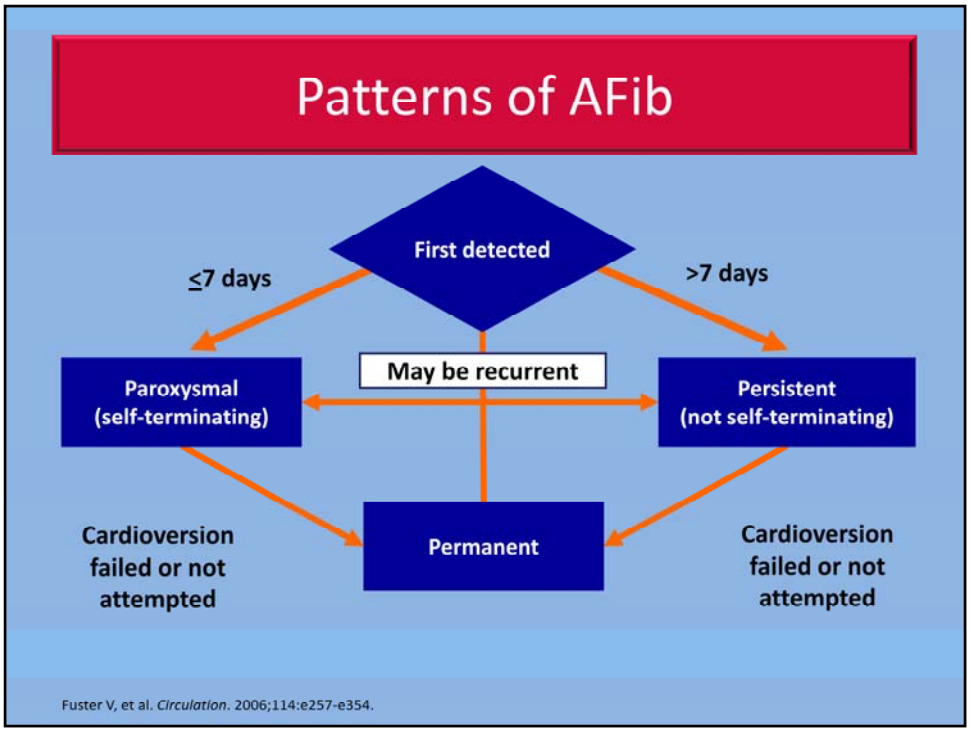
4. Stewart S, Hart CL, Hole DJ, McMurray JJ.A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359-364.
5. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. *J Cardiovasc Electrophysiol*. 2008;19:69-73.

Fuster. Circulation. August.2006/ p265/ Figure 3

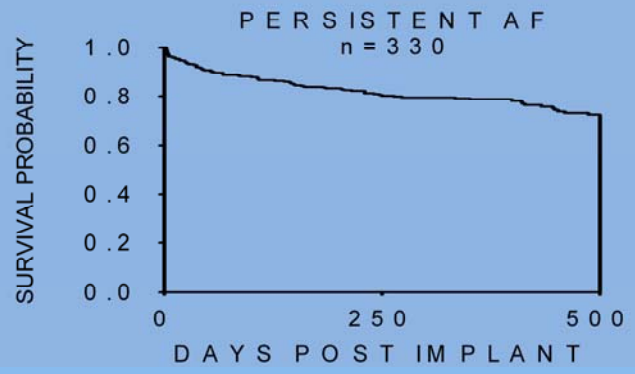



The clinician should distinguish a first-detected episode of AFib, whether or not it is symptomatic or self-limited, recognizing that there may be uncertainty about the duration of the episode and about previous undetected episodes.

Both paroxysmal AFib and persistent AFib are potentially recurrent arrhythmias. With time, paroxysmal AFib may become persistent; likewise, both paroxysmal and persistent AFib may become permanent. (Fuster.Circulation.August.2006/p265/c1/lines 17-22)

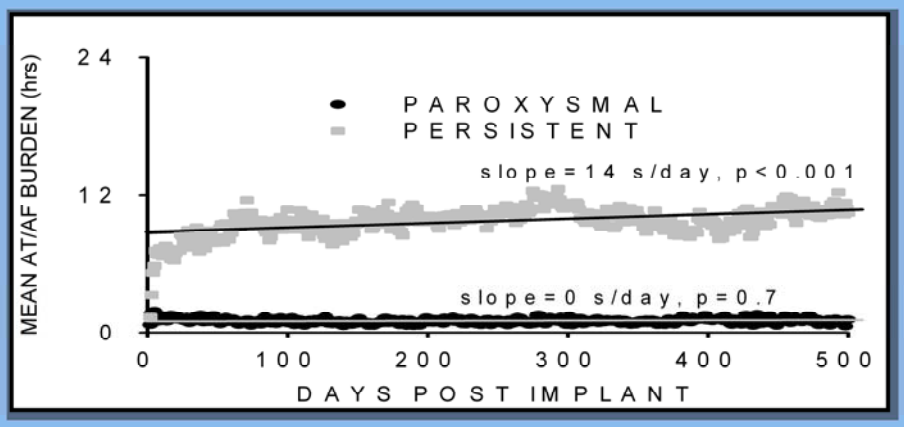
Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.

## Progression of Paroxysmal AFib into Persistent AFib Documented by Pacemaker Datalogs



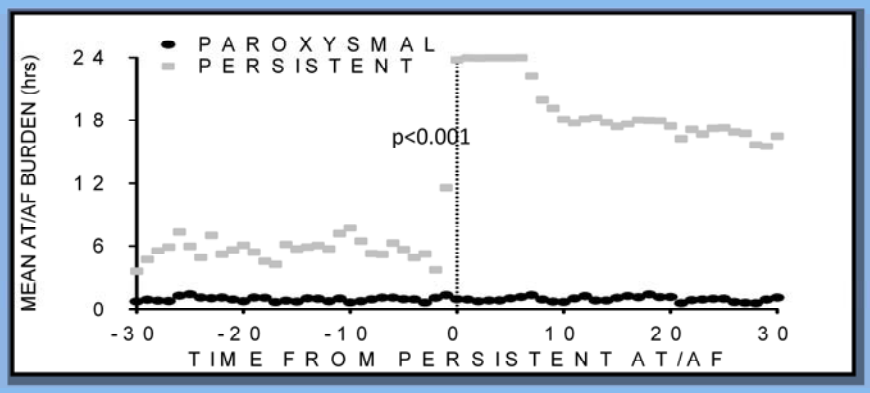

Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L.Am Heart J. 2007 Nov;154(5):884-92

## Progression of Paroxysmal Afib Burden into Persistent AFib Documented by Pacemaker Datalogs



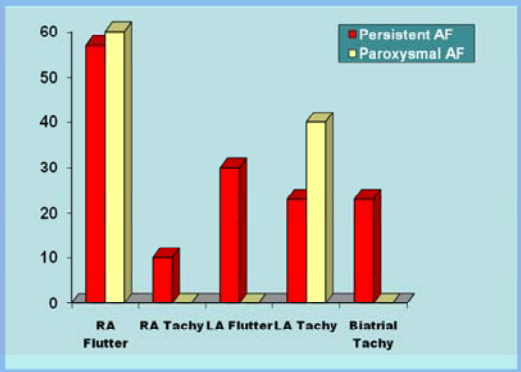

Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L.Am Heart J. 2007 Nov;154(5):884-92

## Conversion of Paroxysmal AFib into Persistent AFib Documented by Pacemaker Datalogs




Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L.Am Heart J. 2007 Nov;154(5):884-92

## Persistent AF is associated with a wider spectrum of Tachycardias than Paroxysmal AF




Spontaneous AT distribution varies with subpopulation

Saksena et al: J. Cardiovasc. Electrophysiol. May 2005

Fuster. Circulation. August.2006/ p275/c1/lines 6-10

Fuster. Circulation. August.2006/ p275/Table 5

Sanfilippo. Circulation.Sept. 1990/p796/c1/ lines 2-13

Therkelsen. J Cardiovasc Mag Reson.2005/p465/ lines A1-A13

Fuster.Circulation. August.2006/p275/ c1/lines 6-10

White.Circ Res. August.1982/p205/ lines A19-A20

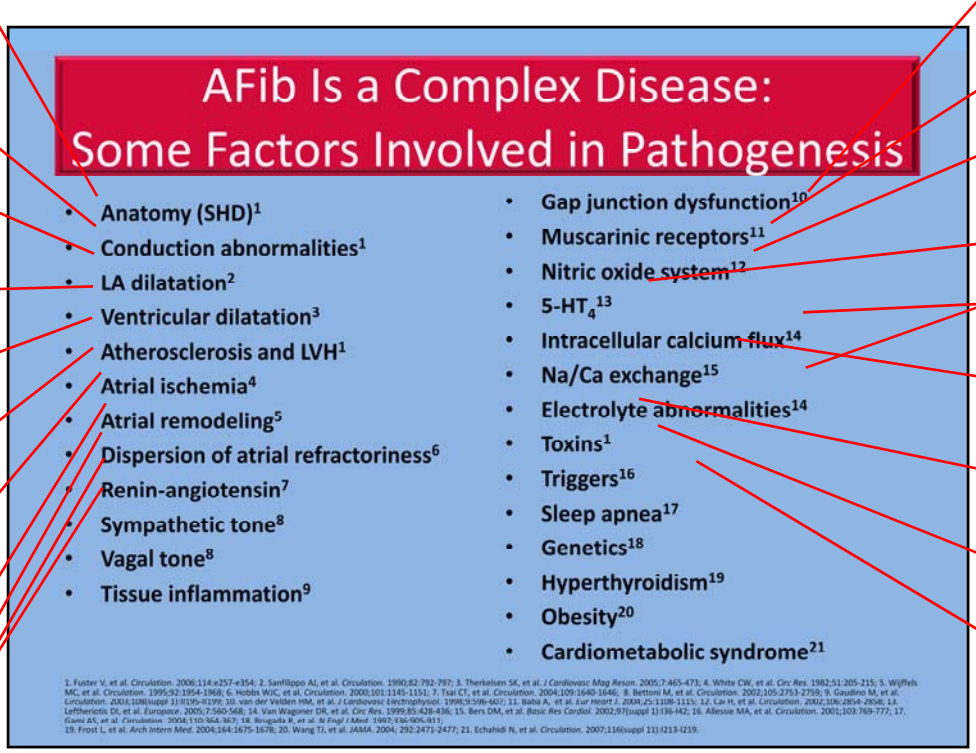
Wijfells.Circulation. Oct.1995/p1954/c2/ lines 25-31

Hobbs.Circ.2000/ p1145/c1/lines 8-13

Tsai.Circulation. April.2004/p1640 lines A1-A17

Bettoni. Circulation. June.2002/ p2753/lines A17-A18

Tissue Inflammation
Gaudino. Circulation. Sept.2003/ pII-195/lines A15-A17




Van der Velden. J Cardiovasc Electrophys.1998/ p596/lines A1-A5

Baba.E Heart J.May. 2004/p1111/c2/ lines 18-22

Cai.Circulation.Nov. 2002/p2854/lines A12-A13

Leftherios.Europace. Sept.2005/p560/ lines A1-A3

van Wagoner.Circ Res. Sept.1999/p428/ lines A3-A14

Bers/Basic Res Cardiol.2002/pI-36/ lines A1-A20

Fuster.Circulation. August.2006/p275/ Table 5

Allessie.Circulation. Feb.2001/p769/c2/ lines 24-30

Gami.Circulation. July.2004/p364/ lines A14-A16

Genetics
Brugada.NEJM.March. 1997/p905/lines A30-36

Specific cardiovascular conditions associated with AFib include valvular heart disease (most often mitral valve disease), HF, coronary artery disease, and hypertension, particularly when LVH.[1] Fuster.Circulation.August.2006/pe275/c1/lines 6-11)

In addition, AFib is commonly encountered in patients with conditions such as sleep apnea syndrome, hyperthyroidism, and obesity. The slide also lists other potential factors involved in the pathogenesis of the disease (ie, changes in vagal tone and tissue inflammation).[1-3] (Fuster.Circulation.August.2006/pe275/Table 5 and pe274/c2/lines 52-53 and pe275/c1/ lines 18-19; Bettoni.Circulation.June.2002/p2753/lines A17-A18; Gaudino.Circulation.September.2003/pII-195/lines A15-A17)

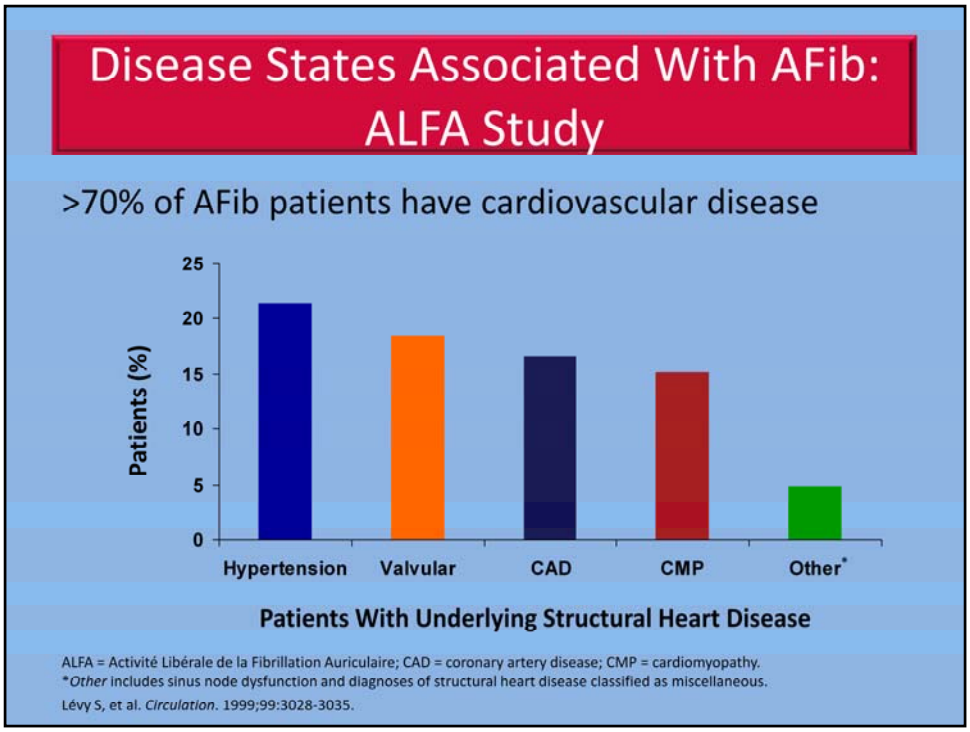
Hyperthyroidism
Frost.Arch Intern Med.Aug.2004/ lines A1-A2

Obesity
Wang.JAMA.Nov. 2004/p2471/ line A30

Cardiometabolic
Echahidi. Circulation.Sept. 2007/pI-213/ lines A17-A18


1. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 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 (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.
2. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation*. 2002;105:2753-2759.
3. Gaudino M, Andreotti F, Zamparelli R, et al.The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation*. 2003;108 Suppl 1:II195-II1199.

Levy. Circulation. June.1999/ p3030/ Table 1



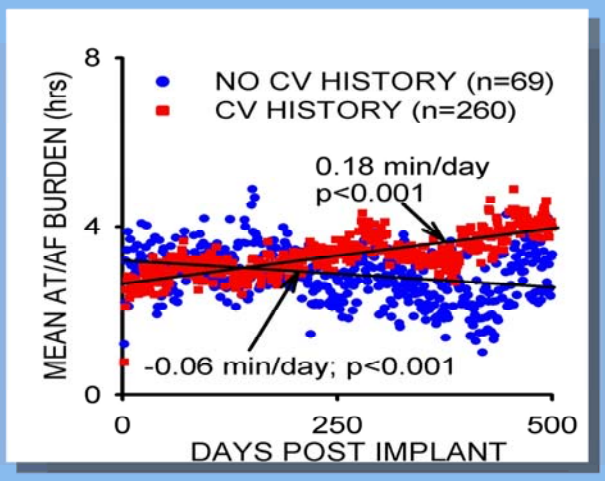

The Activité Libérale de la Fibrillation Auriculaire (ALFA) study was a prospective trial that evaluated the clinical presentations and presence of underlying conditions of French patients with AFib (N=756). (Levy.Circulation.June.1999/p3028/lines A1-A6)

Participants had a documented history of AFib. (Levy.Circulation.June.1999/p3028/A4-A6) Patient follow-up was conducted at 6- and 12-month intervals. (Levy.Circulation.June.1999/p3029/c1/line 27)

The majority of patients (88.6%) were symptomatic. (Levy.Circulation.June.1999/p3028/line A6) Moreover, underlying heart disease was present in 70.6% of patients. (Levy.Circulation.June.1999/p3034/c1/lines 13-14) Hypertension (21.4%), valvular disorders (18.5%), CAD (16.6%), and cardiomyopathy (15.2%) were the most commonly observed forms of underlying cardiac disease in those with AFib. (Levy.Circulation.June.1999/p3030/Table 1)

Lévy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. *Circulation*. 1999;99:3028-3035.

# AFib Burden Progressively Increases with Cardiovascular Disease

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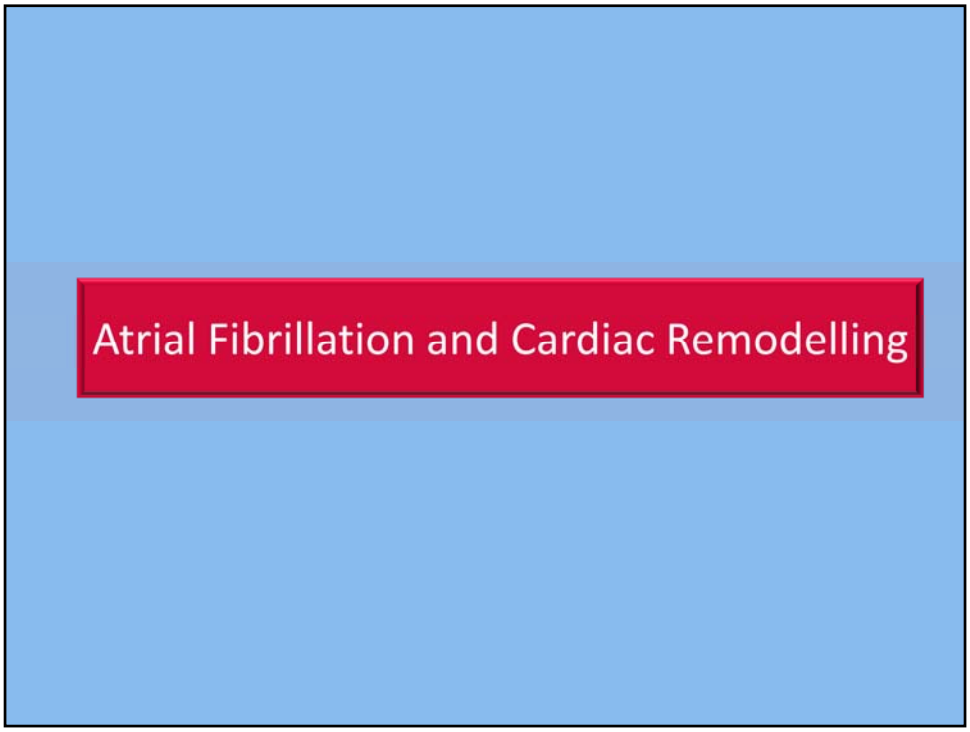
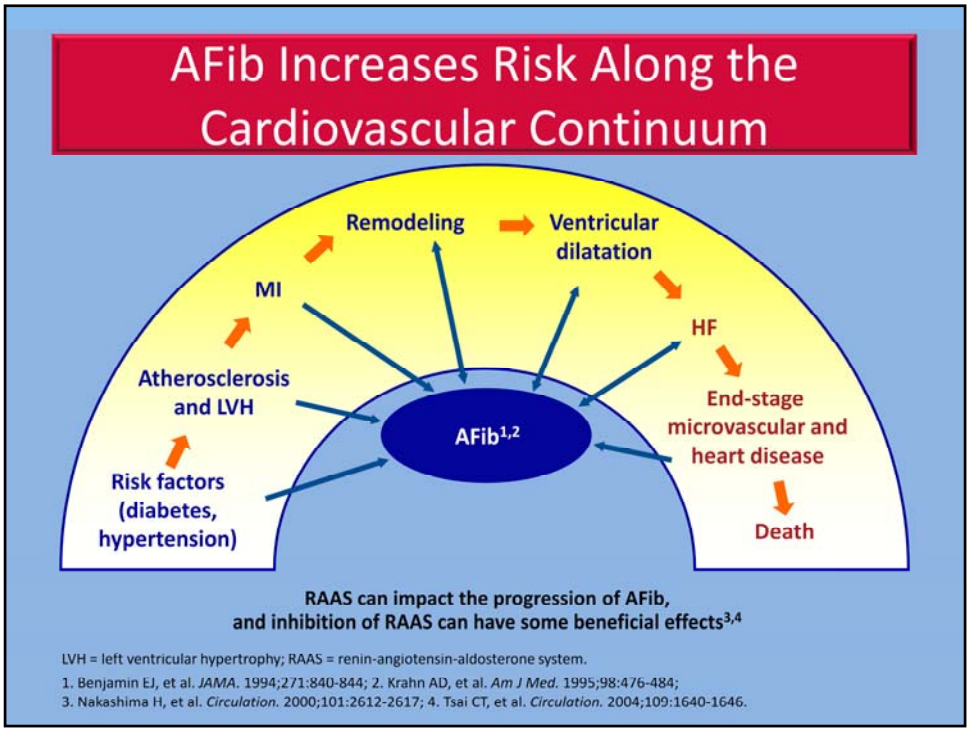


Benjamin. JAMA.March. 1994/p840/ lines A23-A26

Krahn. Am J Med.May.1995/ c2/p476/ lines A1-A3




Nakashima. Circulation. June. 2000/ p2612/lines A13-A15

Tsai.Circulation. April.2004/lines A1-A7

AFib can be present with, be affected by, and serve as a contributing factor in a wide range of cardiovascular conditions. Risk factors for cardiovascular disease (eg, hypertension and diabetes) also predispose patients to AFib. Additionally, AFib may increase the risk of cardiovascular disease.[1,2] (Benjamin.JAMA.March.1994/p840/lines A23-A26; Krahn.Am J Med.May.1995/c2/p476/lines A1-A3)

Several renin-angiotensin-aldosterone system (RAAS) pathways are activated in experimental models of AFib as well as AFib patients. Furthermore, inhibition of angiotensin-converting enzyme and blockade of angiotensin II receptor may potentially prevent AFib by reducing fibrosis.[3,4] (Nakashima.Circulation.June.2000/p2612/lines A13-A15; Tsai.Circulation.April.2004/p1640/lines A1-A17) Therefore, modification of risk factors for cardiovascular disease may decrease the incidence of AFib.[1] (Benjamin.JAMA.March.1994/p840/lines A23-A26)

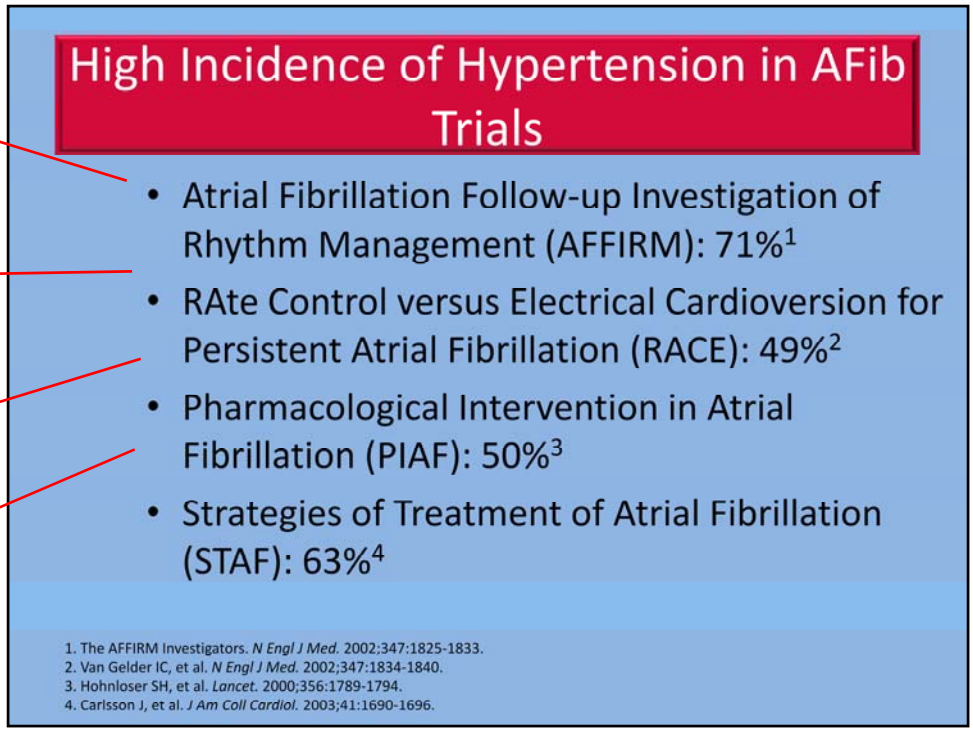

1. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840-844.
2. Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-up Study. *Am J Med.* 1995;98:476-484.
3. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodelling in atrial fibrillation. *Circulation.* 2000;101:2612-2617.
4. Tsai CT, Lai LP, Lin JL, et al. Renin-angiotensin system gene polymorphisms and atrial fibrillation. *Circulation.* 2004;109:1640-1646.

AFFIRM. NEJM. December. 2002/p1825/ lines A16-A17

Van Gelder. NEJM. December. 2002/p1836/ Table 1

Hohnloser. Lancet. November. 2000/p1790/ Table 1

Carlsson. JACC.May. 2003/p1692/ Table 1



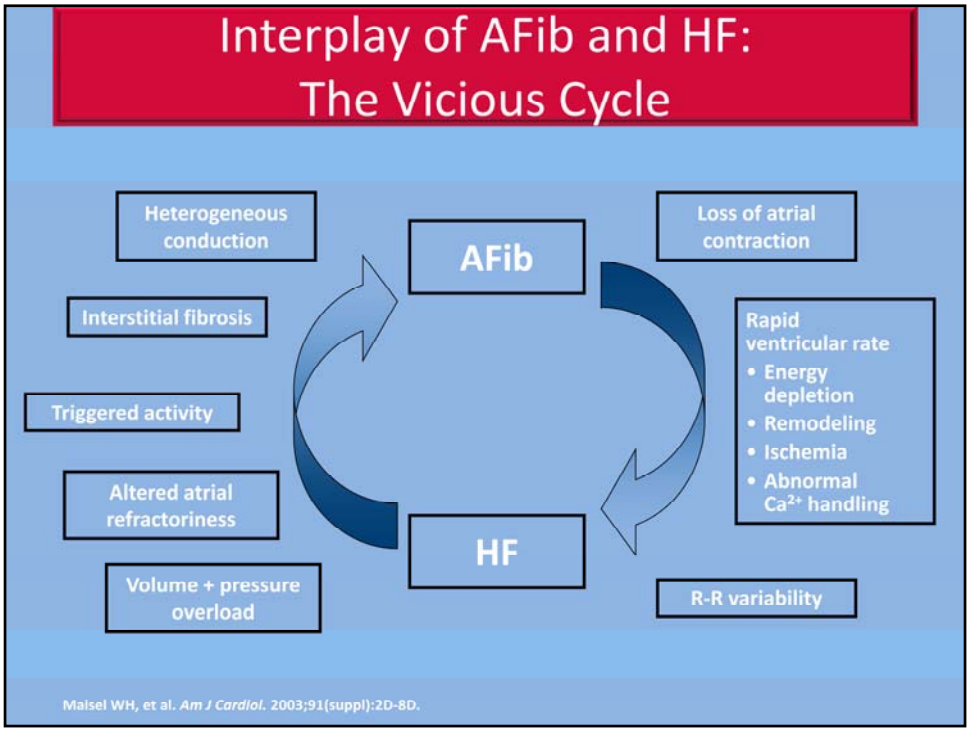

Atrial fibrillation is often associated with other cardiovascular diseases, most commonly hypertension and ischemic heart disease. Hypertension may increase atrial dilatation, leading to both AFib and the formation of left atrial thrombi.[1]

**(Wyse.Circulation.June.2004/p3093/c1/lines 29-31)**

Moreover, hypertension is an independent risk factor for the development of AFib and stroke.[2] **(Benjamin.JAMA.March.1994/p840/lines A6-A9)** A number of AFib clinical trials have found a high incidence of hypertension.[3-6] **(AFFIRM.NEJM.December.2002/p1825/lines A16-17; Van Gelder.NEJM.December.2002/ p1836/Table 1; Hohnloser.Lancet.November.2000/p1790/Table 1; Carlsson.JACC.May.2003/p1692/Table 1)** Therefore, management of hypertension may reduce the burden of AFib.


1. Wyse DG, Gersh BJ. Atrial fibrillation: a perspective: thinking inside and outside the box. *Circulation*. 2004;109;3089-3095.
2. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;16:840-844.
3. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825-1833.
4. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834-1840.
5. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation–Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet*. 2000;356:1789-1794.
6. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: The Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol.* 2003;41:1690-1696.

Maisel.
Am J Cardiol.
March.2003/
p5D/Figure 2

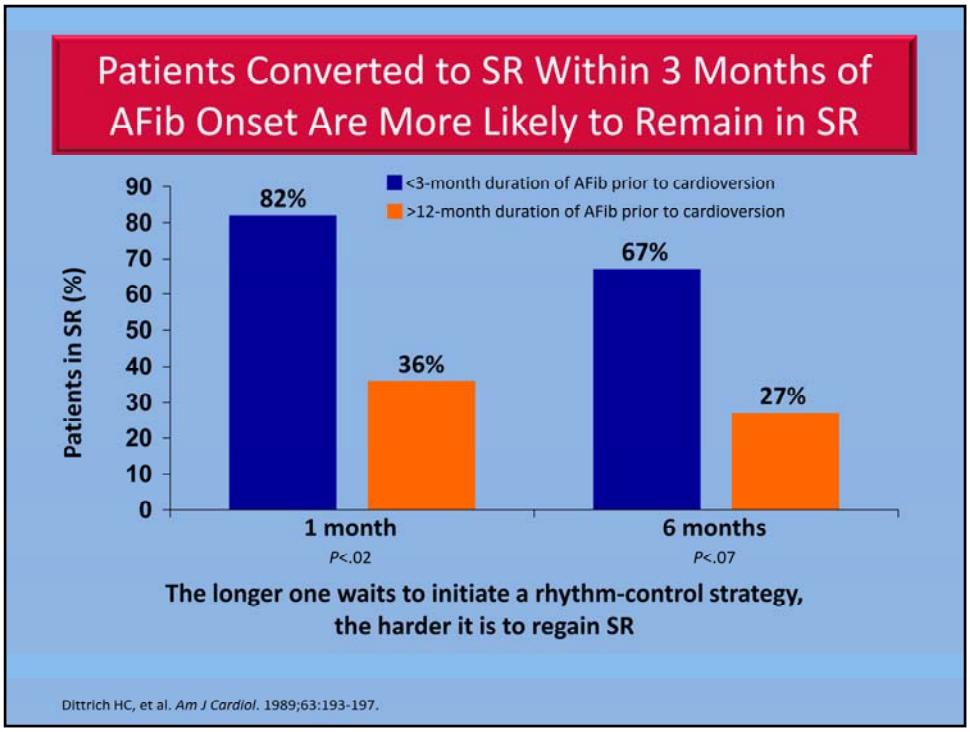



Heart failure can cause atrial changes that may either predispose to or worsen AFib. Heart failure can also cause a number of neurohormonal alterations. Activation of the renin-angiotensin-aldosterone system can lead to interstitial fibrosis, which may cause further conduction delay. (Maisel.Am J Cardiol.March.2003/p3D/c2/lines 28-37) Essentially, any change that decreases the atrial refractory period, slows atrial conduction, or increases heterogeneity of atrial repolarization can propagate AFib. (Maisel.Am J Cardiol.March.2003/p3D/c2/lines 8-17)

Conversely, AFib can lead to HF. The hemodynamic changes that result from AFib can lead to further deterioration of cardiac function by reducing stroke volume, cardiac output, and peak oxygen consumption. Additionally, the irregular ventricular response that is characteristic of AFib may also affect ventricular function and hemodynamic status. Finally, remodeling at the cellular level (ie, ion-channel function) may affect atrial conduction and repolarization. This may promote the maintenance of AFib.
(Maisel.Am J Cardiol.March.2003/p4D/c1/lines 33-59)

Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91(suppl):2D-8D.

Dittrich. AJC.January. 1989/p195/ Figure 2 & p195/c1/lines 1-6



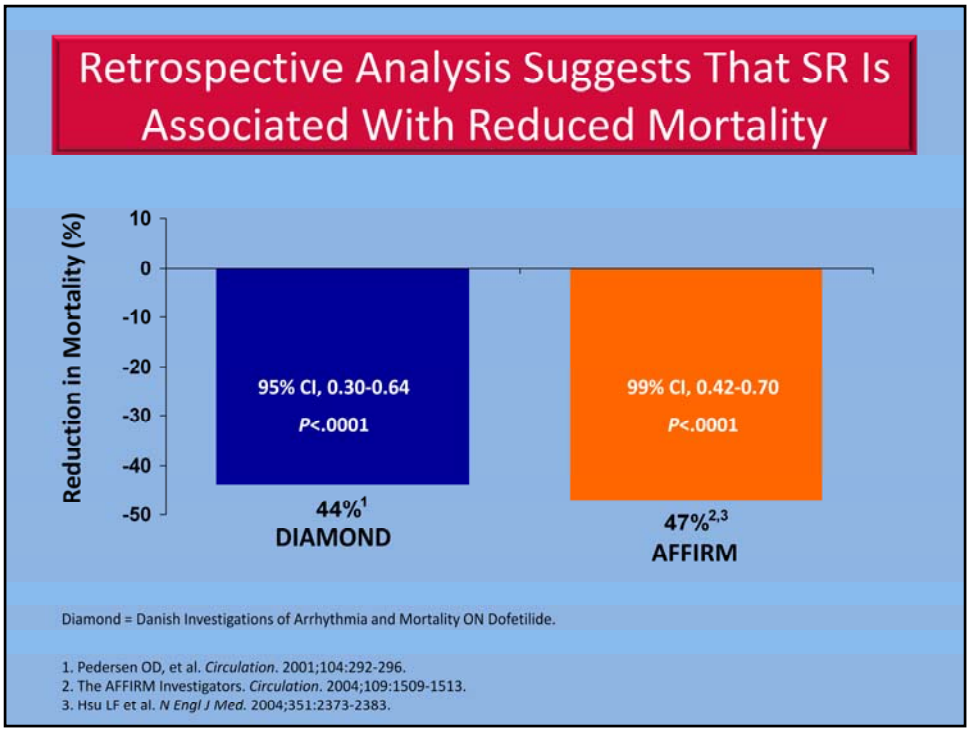

Dittrich and colleagues evaluated echocardiographic and clinical features in patients with AFib that had been converted to SR (N=85) to determine predictors of success in maintaining SR. (Dittrich. AJC.January.1989/p193/lines A1-A36)

Among the patients with AFib of less than 3 months' duration prior to cardioversion, 82% remained in SR 1 month after cardioversion, compared with 36% of those whose AFib had been present for more than12 months ($P$<0.02). (Dittrich. AJC.January.1989/p195/Figure 2 & p195/c1/lines 1-6)

The investigators found that the duration of AFib may predict the maintenance of SR at 1 month after successful cardioversion. (Dittrich. AJC.January.1989/p193/lines A28-A36)

Dittrich HC, Erikson JS, Schneiderman T, Blacky AR, Savides T, Nicod PH. Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. *Am J Cardiol*. 1989;63:193-197.

Pedersen. Circulation. July.2001/ p294/c2/ lines 9-11




AFFIRM Investigators. Circulation. March.2004/ p1511/Table 3 & p1511/c1/ lines 29-30

Hsu.NEJM. December. 2004/p2381/ c1/lines 3-6

Results of several retrospective analyses have suggested that SR may be associated with reduced mortality.[1,2] (Pedersen.Circulation.July.2001/p294/c2/lines 9-11 & AFFIRM Investigators. Circulation.March.2004/p1509/lines A13-A14) A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) substudy sought to determine whether dofetilide could restore and maintain SR and reduce mortality and hospitalizations in patients (N=506) with AFib or atrial flutter.[1] (Pedersen.Circulation.July.2001/p292/lines A1-A6) Although dofetilide had no effect on all-cause mortality, restoration and maintenance of SR was associated with a significant reduction in mortality (RR, 0.44; 95% CI, 0.30-0.64, *P*<.0001).[1] (Pedersen.Circulation.July.2001/p292/lines A8-A9)

A substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study was used for an "on-treatment" analysis of the relationship of survival to cardiac rhythm and treatment as they changed over time.[2] (AFFIRM Investigators.Circulation. March.2004/p1509/lines A3-A4) Compared with AFib, restoration and maintenance of SR was associated with a 47% reduction in the risk of death.[3] (Hsu.NEJM.December.2004/p2381/c1/lines 3-6) In this trial, the beneficial effects of AADs may have been offset by their adverse effects.[2] (AFFIRM Investigators.Circulation. March.2004/p1509/lines A15-A17) These results suggest that if an effective method of maintaining SR with fewer adverse events were available, survival might be improved.[2] (AFFIRM Investigators.Circulation.March.2004/p1513/c1/lines 45-47)

1. Pedersen OD, Bagger H, Keller N, et al. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) substudy. *Circulation*. 2001;104:292-296.
2. The AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation*. 2004;109:1509-1513.
3. Hsu LF, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373-2383.

# Retrospective Analysis Suggests That SR Is Associated With Reduced Mortality: CHF - STAT

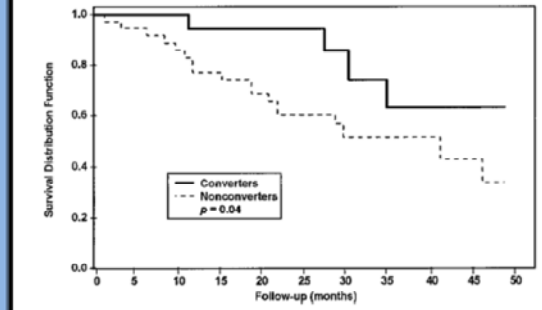
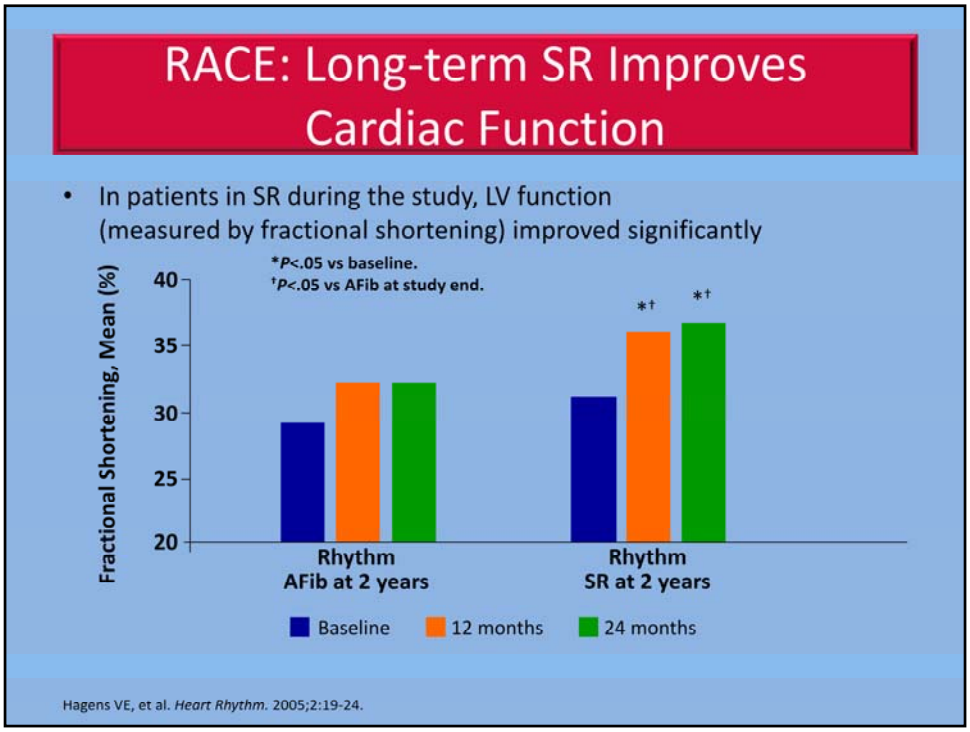



**Figure 3.** Kaplan-Meier analysis of survival curves in heart failure patients with AF who converted (n=16) and did not convert (n=35) to sinus rhythm on treatment with amiodarone. Note that survival was significantly better in those who converted to sinus rhythm during the course of follow-up.

Hagens. HeartRhythm. January.2005/ p 22/Fig. 1

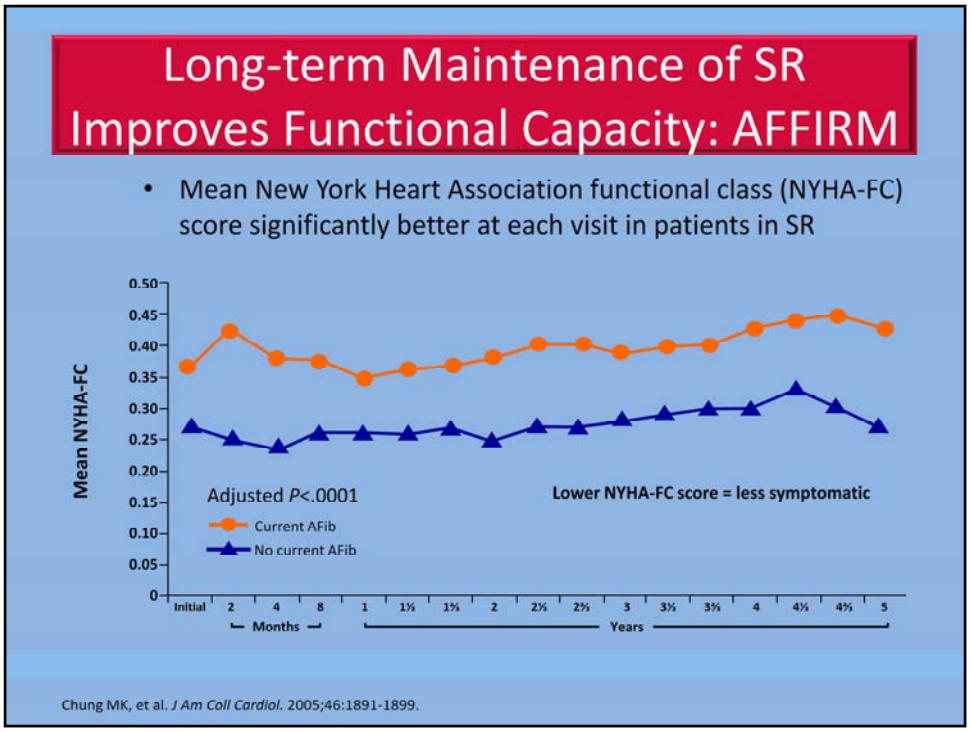



Patients in the RAte Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study (N=335) were echocardiographically evaluated to determine whether restoration of SR in patients with AFib would improve left ventricular (LV) function and reduce atrial dimensions. (Hagens.HeartRhythm.January.2005/p19/lines A1-A7) Echocardiography was performed at baseline and at 1- and 2-year follow-up evaluations. Results were compared for those assigned to the rhythm-control arm (n=175) and those assigned to the rate-control arm (n=160). Additionally, for the rhythm-control group, echocardiographic findings were compared between those in AFib and those in SR at the end of the study. (Hagens.HeartRhythm.January.2005/p19/lines A1-A9)

Thirty-four percent of patients in the rhythm-control arm were in SR at the end of the study. There was significant improvement in LV function, as measured by fractional shortening, in patients who were in SR at 2 years (*P*<.05 vs AFib). (Hagens.HeartRhythm.January.2005/p21/c1/lines 28-32) The study investigators concluded that maintenance of SR is associated with improvement in LV function and reduction in atrial size. (Hagens.HeartRhythm.January.2005/p19/lines A17-A18)

Hagens VE, Van Veldhuisen DJ, Kamp O, et al. Effect of rate and rhythm control on left ventricular function and cardiac dimensions in patients with persistent atrial fibrillation: results from the RAte Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study. *Heart Rhythm*. 2005;2:19-24.

Chung.JACC. November.2005/ p1893/ C2/ lines19-34 & p1895, Figure 1B



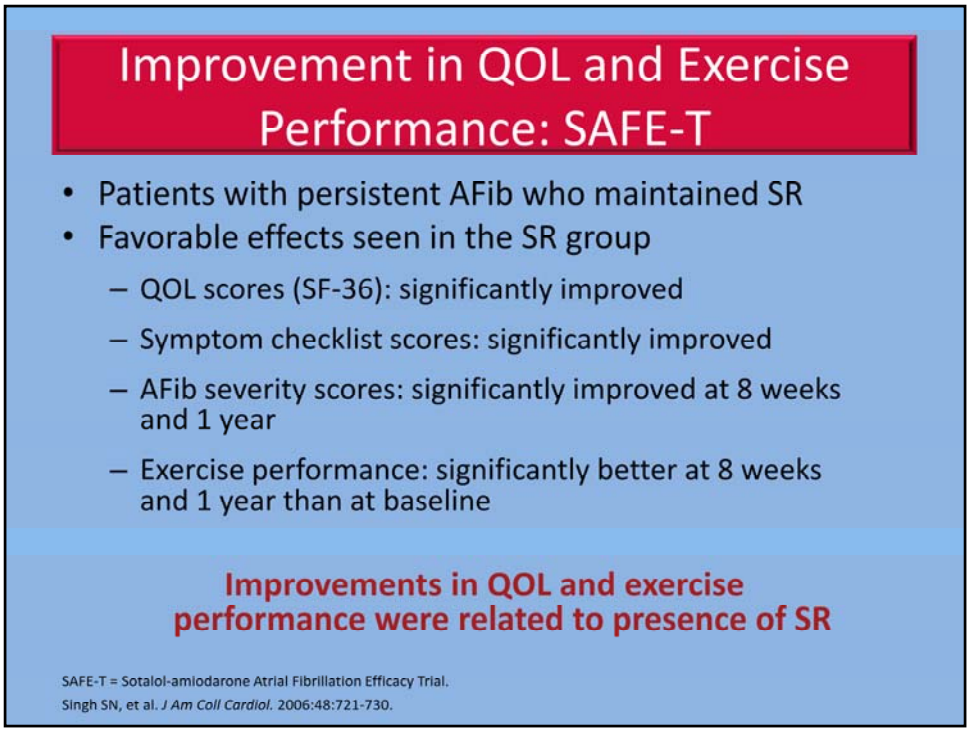

The AFFIRM functional status substudy was designed to determine if long-term maintenance of SR is associated with improved functional capacity. (Chung.JACC.November.2005/p1891/lines A1-A3) All patients (N=245) had AFib and required long-term therapy. Additionally, patients were older than 65 years or had another risk factor for stroke and death. Patients were randomized to either rate control or rhythm control. (Chung.JACC.November.2005/p1891/lines A8-A15)

Canadian Cardiovascular Society Angina Classification and New York Heart Association functional class (NYHA-FC) were assessed at baseline, 2-month, and yearly visits. The participants underwent a 6-minute walk test and the Mini-Mental State Examination at each visit as well. (Chung.JACC.November.2005/p1891/lines A12-A15) No differences were observed in the Canadian Cardiovascular Society Angina Classification or Mini-Mental State Examination scores. The 6-minute walk distance improved over time in both study arms. (Chung.JACC.November.2005/p1891/lines A16-A20)

However, an adjusted analysis of NYHA-FC across all visits demonstrated that the presence of AFib was associated with significantly worse NYHA-FC (*P*<.0001). (Chung.JACC.November.2005/p1893/c2/lines 19-23) Therefore, long-term maintenance of SR in patients with AFib may result in functional improvement. (Chung.JACC.November.2005/p1898/c2/lines 3-7)

Chung MK, Shemanski L, Sherman DG, et al. Functional status in rate- versus rhythm-control strategies for atrial fibrillation. *J Am Coll Cardiol*. 2005;46:1891-1899.

Singh.JACC. August.2006/ p721/ lines A1-A20



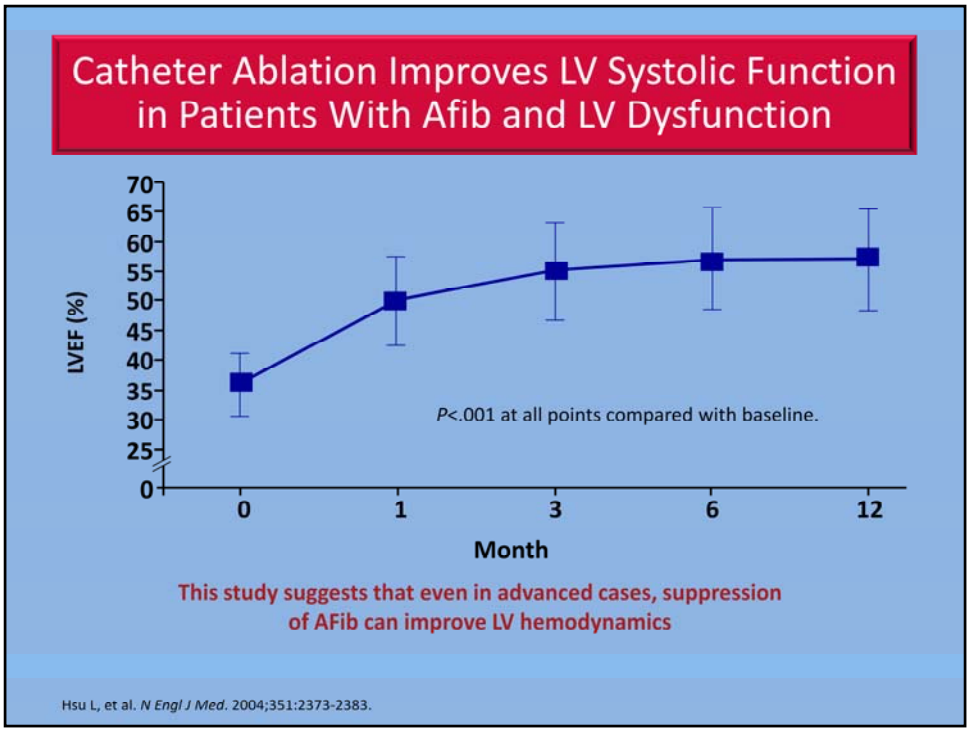

SAFE-T was a randomized, double-blind, multicenter, placebo-controlled trial in which the efficacy of sotalol and amiodarone in maintaining SR in patients (N=665) with persistent AFib were examined. The primary end point was the time to recurrence of AFib as determined by weekly transtelephonic monitoring. The median times to a recurrence of AFib were 487 days in the amiodarone group, 74 days in the sotalol group, and 6 days in the placebo group according to intention to treat and 809, 209, and 13 days, respectively, according to treatment received. Amiodarone was superior to sotalol (*P*<.001) and to placebo (*P*<.001), and sotalol was superior to placebo (*P*<.001).[1] (Singh.NEJM.May.2005/p1861/lines A1-A28)

Singh and colleagues performed a substudy of the Sotalol-amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) to evaluate whether maintenance of SR was associated with improvements in QOL and exercise tolerance.[2] (Singh.JACC.August.2006/p721/lines A1-A3)

In this substudy the following were evaluated: QOL (SF-36), Symptom Checklist (SCL), Specific Activity Scale, Atrial Fibrillation Severity Scale (AFSS), and exercise performance. The scores for SCL severity, functional capacity, and AFSS symptom burden at 8 weeks and for SCL severity and AFib symptom burden at 1 year showed significant improvements with SR vs AFib; symptomatic patients were more likely to have improvement. Exercise performance was greater from baseline to 8 weeks (*P*=.01) and to 1 year (*P*=.02) with SR vs AFib. These data suggest that in patients with persistent AFib, restoration and maintenance of SR may be associated with improvements in QOL measures and exercise performance.[2] (Singh.JACC.August.2006/p721/lines A5-A20)

1. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med.* 2005;352:1861-1872.
2. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program substudy. *J Am Coll Cardiol*. 2006;48:721-730.

Hsu.NEJM.2004/
p2378/Figure 1A



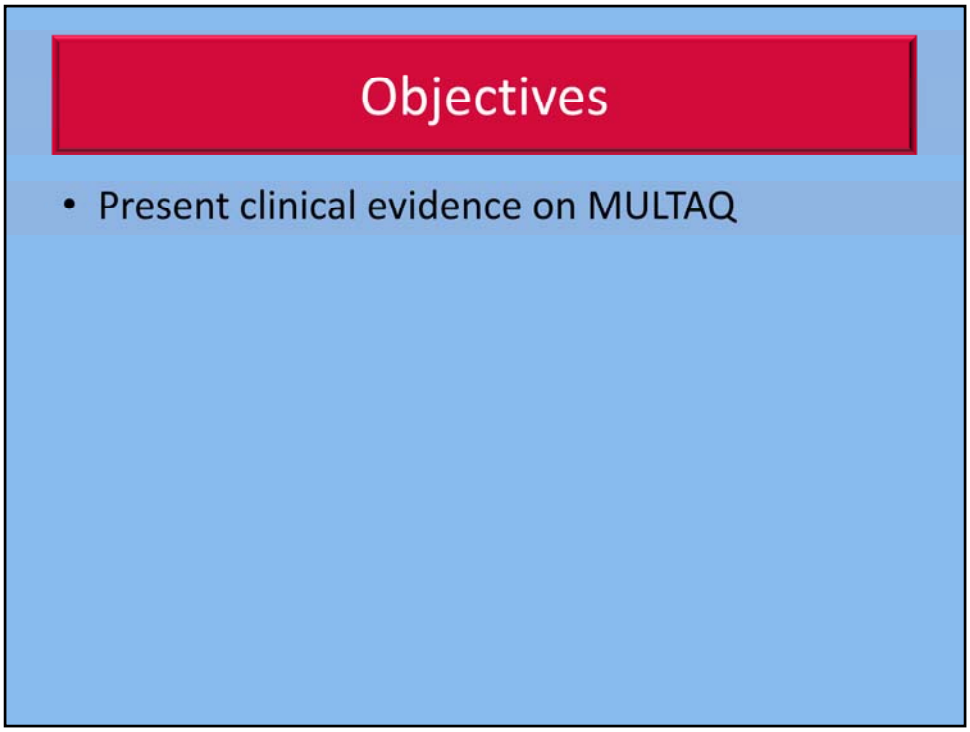

Hsu.NEJM.2004/
p2373/
lines A29-A31

Hsu and colleagues compared patients with CHF and LVEF below 45% who were about to undergo catheter ablation for AFib (n=58) with matched controls with AFib (n=58) to evaluate their LV function, symptom score, exercise capacity, and QOL. **(Hsu.NEJM.2004/p2373/lines A1-A31)**

After catheter ablation, patients were followed for an average of 1 year. Sinus rhythm was maintained in 78% of the patients with CHF and in 84% of the controls (*P*=.34). The patients with CHF had significant improvement in LV function (increases in the ejection fraction and fractional shortening of 21% and 11%, respectively; *P*<.001 for both), LV dimensions, exercise capacity, symptoms, and QOL. **(Hsu.NEJM.2004/p2378/Figure 1A & p2373/lines A1-A27)**

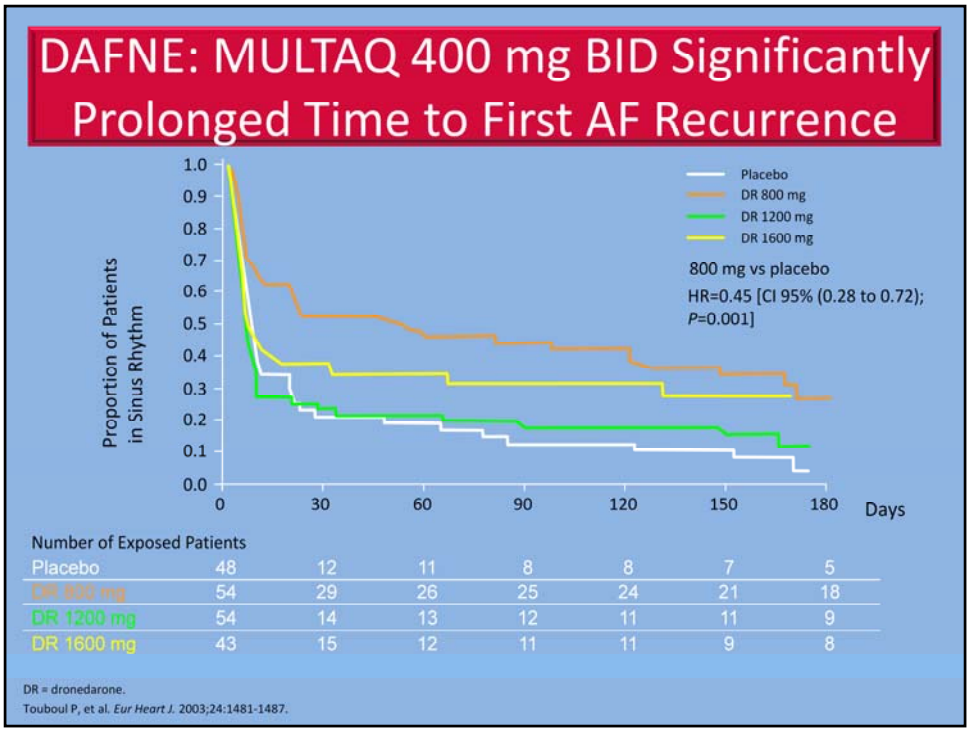
These results suggest that maintenance of SR with catheter ablation in patients with CHF and AFib can significantly improve cardiac function, symptoms, exercise capacity, and QOL. **(Hsu.NEJM.2004/p2373/lines A29-A31)**

Hsu LF, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373-2383.




The objectives for this presentation are as follows:
To review the current state of atrial fibrillation
To present clinical data on MULTAQ and to understand the inappropriate and appropriate patient selection for treatment with MULTAQ

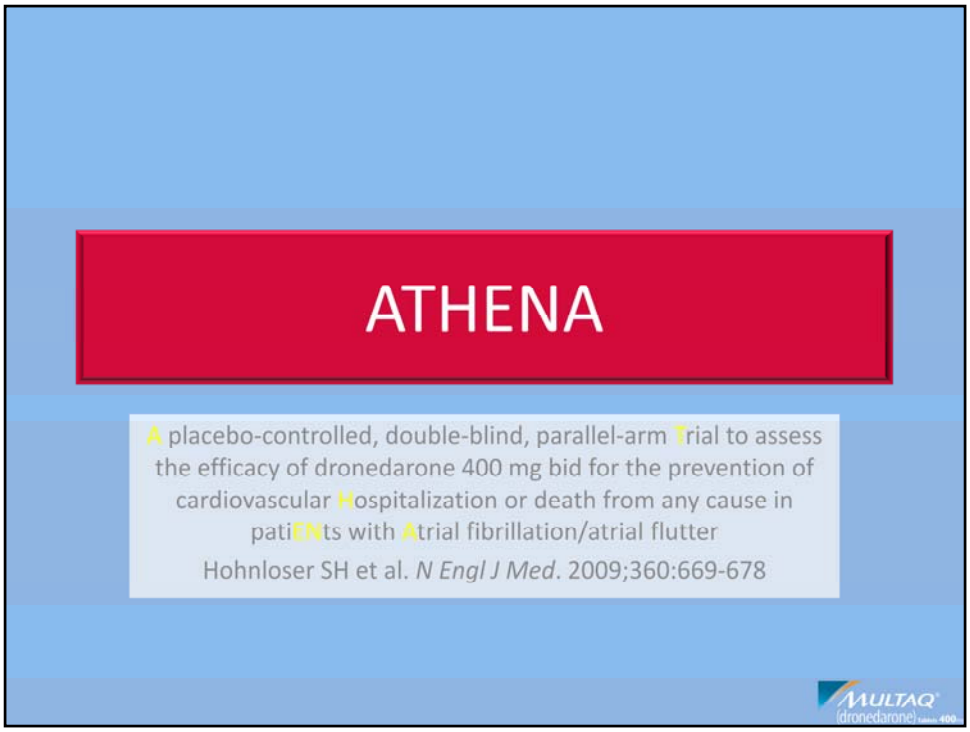
Touboul, Eur Heart J, 2003, p1483, fig 1




DAFNE demonstrated that MULTAQ at 400 mg BID (800 mg total dose) significantly prolonged time to first atrial fibrillation recurrence, compared with placebo. **(Touboul, Eur Heart J. 2003, p1482/col 2/lines 50-53)**

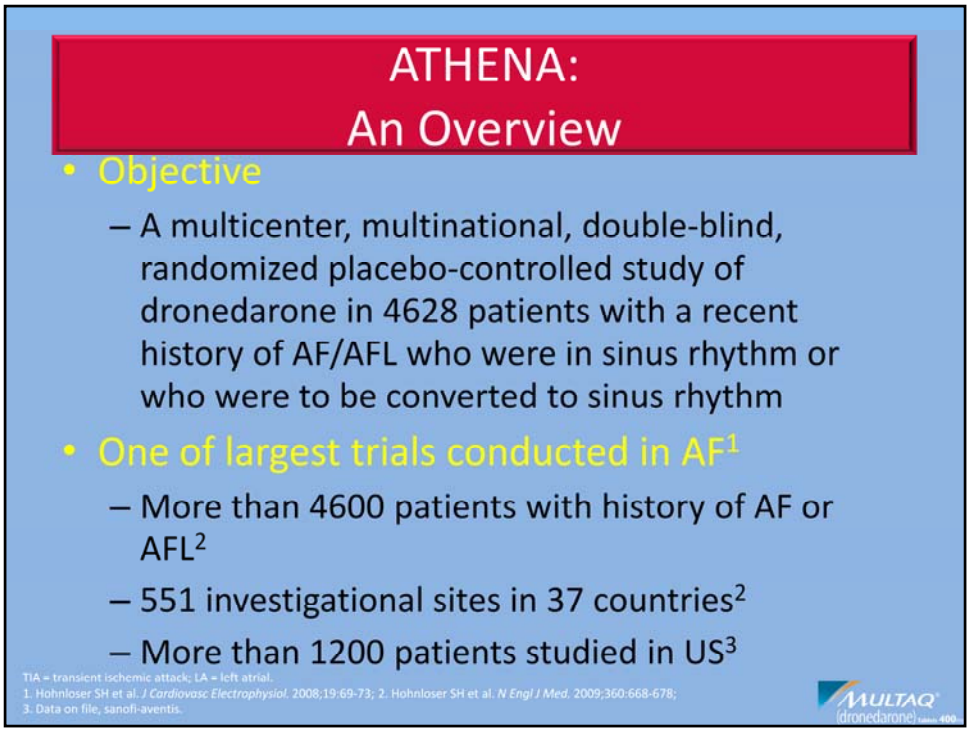
Higher doses did not show significantly better efficacy than placebo. **(Touboul, Eur Heart J. 2003, p1482/col 2/lines 56-57 and p1483/col1/line 1)**

Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J.* 2003;24:1481-1487.



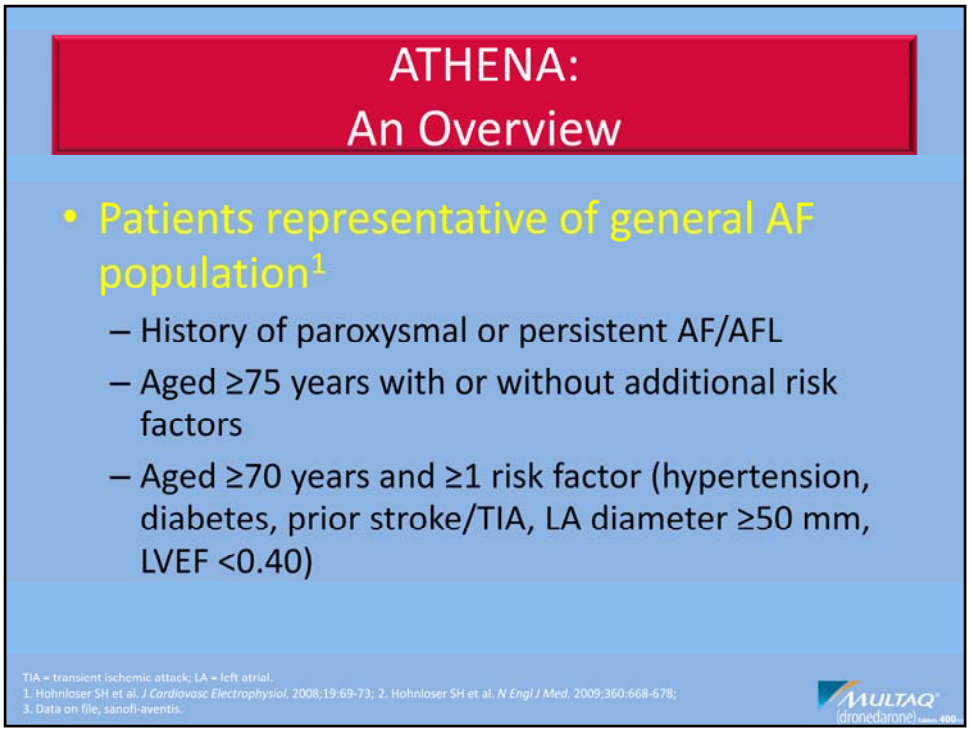

ATHENA (**A** Placebo-Controlled, Double-Blind, Parallel Arm **T**rial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular **H**ospitalization or Death from Any Cause in Pati**EN**ts with **A**trial Fibrillation/Atrial Flutter) was designed to determine whether dronedarone would reduce the rate of the composite outcome of hospitalization due to CV events or death in patients with AF

Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360:668-678.




One of the key trials for MULTAQ was the ATHENA trial[1]
ATHENA was a large—landmark—outcomes trial and unique in several ways: with more than 4600 patients and 551 investigators in 37 countries, it is the largest single antiarrhythmic drug trial ever conducted in AF[1,2]
Patients enrolled in ATHENA were representative of the AF population[1]
ATHENA was a prospective, randomized, placebo-controlled, double-blind, multinational, multicenter, parallel-group trial with a 30-month maximum duration. Patients enrolled had paroxysmal or persistent AF or AFL with a recent episode (in the last 6 months) and were in sinus rhythm or to be cardioverted at randomization[3]
MULTAQ was initiated following discontinuation of antiarrhythmics, and 30 days after discontinuation of a class III antiarrhythmic. ATHENA excluded patients who had either hemodynamic instability or severe (NYHA class IV) heart failure[3]

1. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. *J Cardiovasc Electrophysiol.* 2008;19:69-73.
2. Hohnloser SH, Crijns HJ, van Eikels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360:668-678.
3. Data on file, sanofi-aventis.

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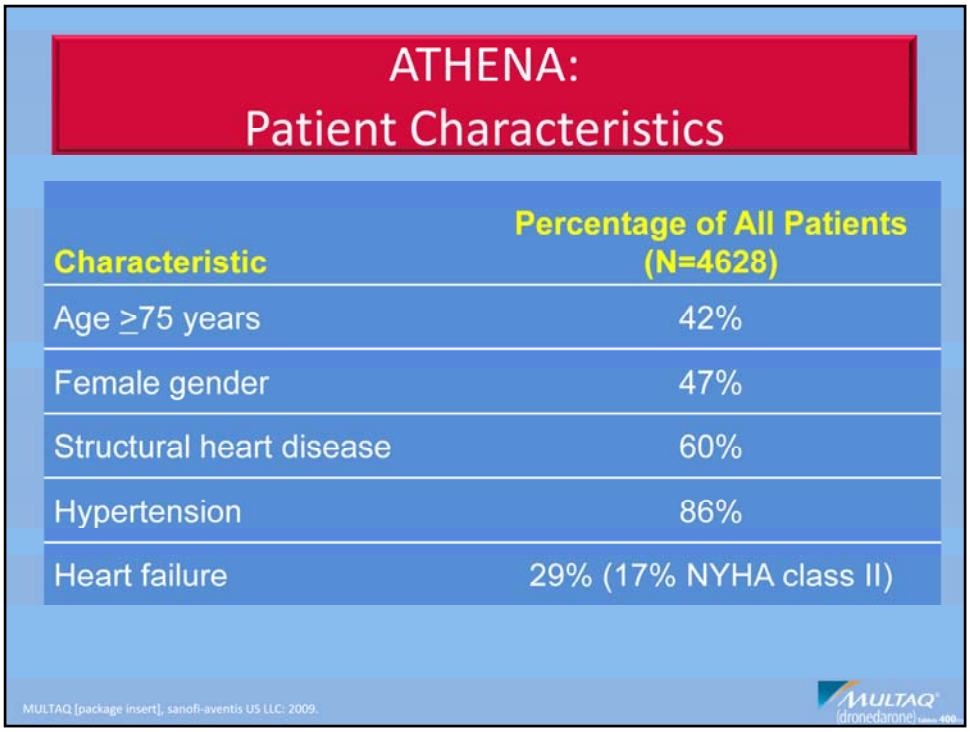
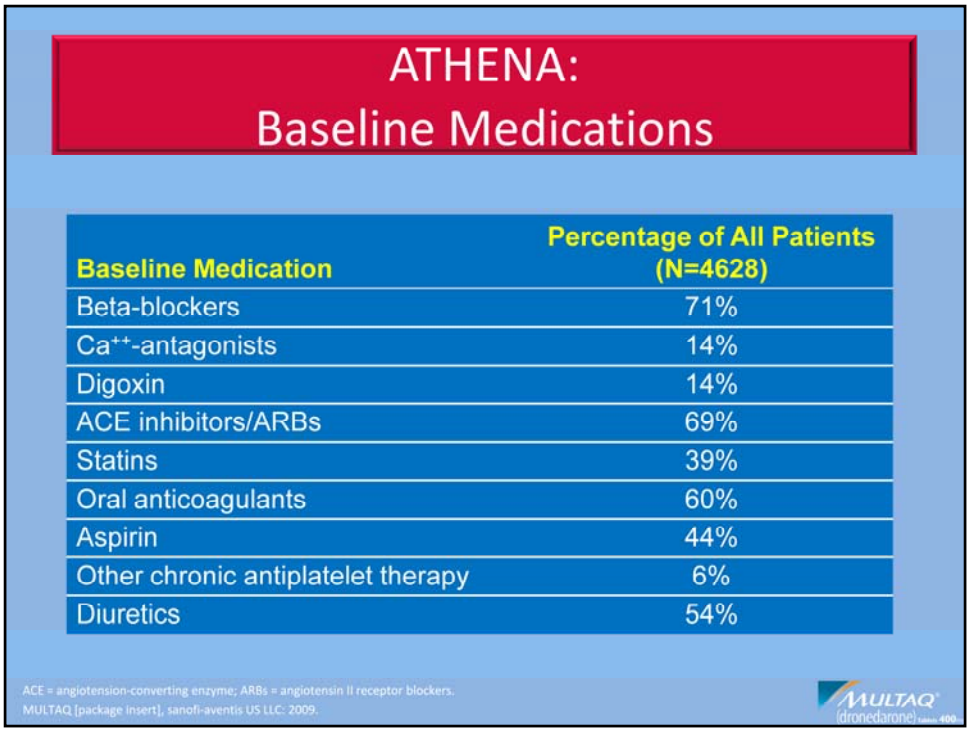



A total of 4628 patients were enrolled, of whom 2301 were randomly assigned to receive dronedarone and 2327 to receive placebo

The overall patient study population had the following baseline characteristics:

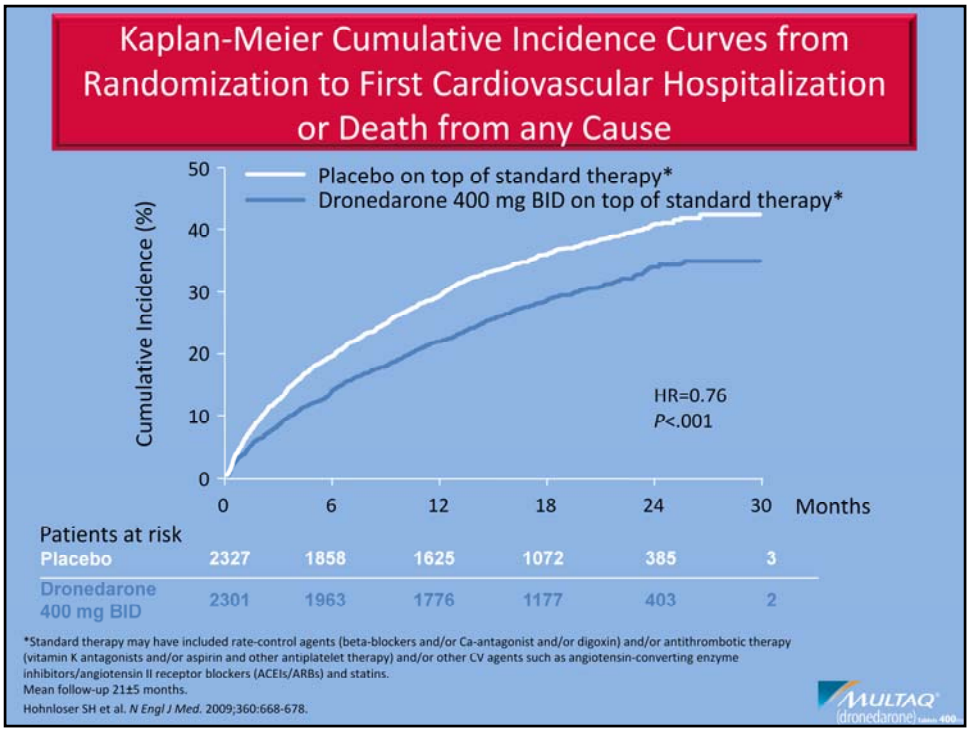
- Patient age ranged from 23 to 97 years, and 42% of patients were ≥75 years of age
- 47% of study subjects were female and the majority (89%) were Caucasian
- The predominant underlying CV disease was hypertension (86%), and there was evidence of structural heart disease in 60% of patients
- The median LVEF was 60%; 29% of patients had heart failure, mostly NYHA class II (17%)

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.



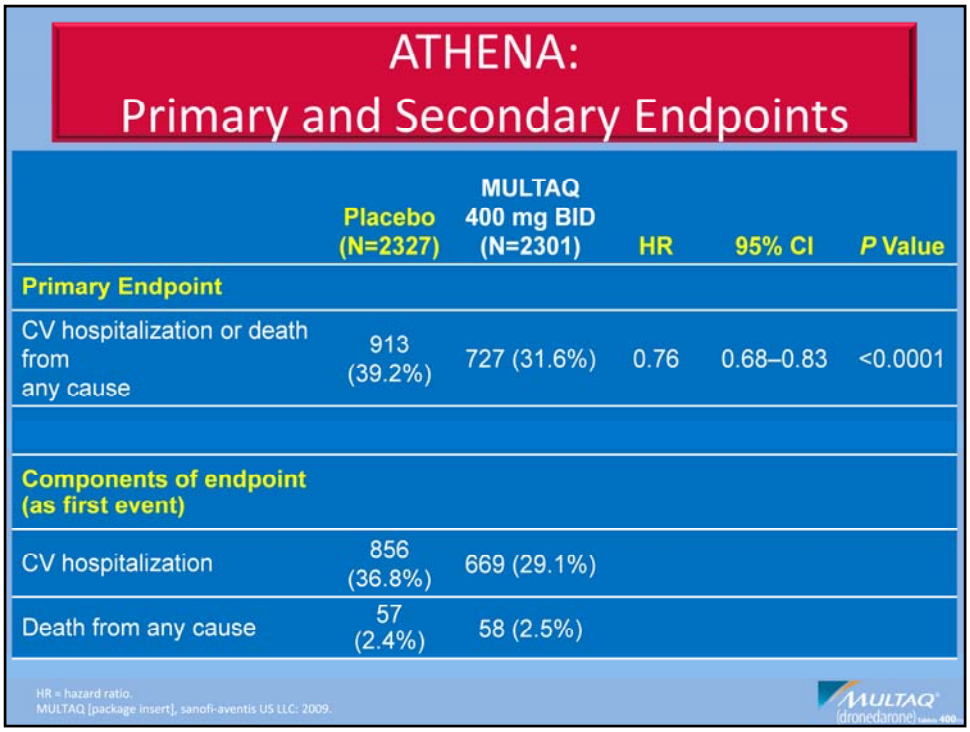

Baseline medications for ATHENA patients included beta-blockers (71%), calcium antagonists (14%), digoxin (14%), ACE inhibitors or ARBs (69%), statins (39%), oral anticoagulants (60%), aspirin (44%), other chronic antiplatelet therapy (6%), and diuretics (54%)

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.



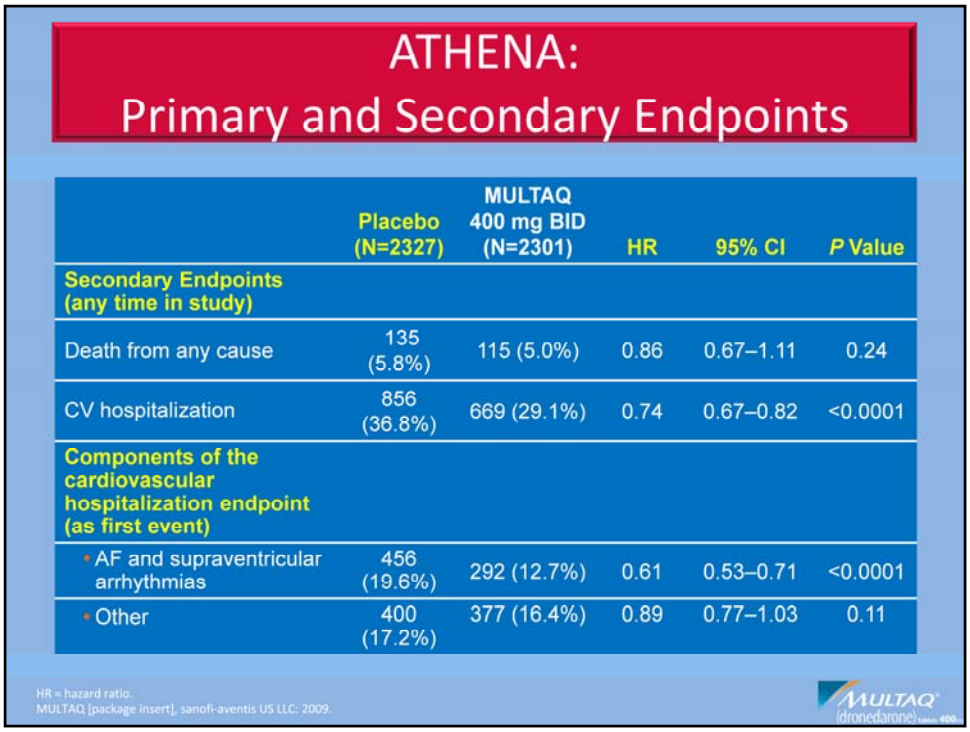

ATHENA met its primary endpoint of reduction in cardiovascular hospitalizations or death from any cause.
MULTAQ reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo. This difference was entirely attributable to its effect on cardiovascular hospitalization, principally hospitalization related to AF

Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360:668-678.




This chart lists the incidence of primary and secondary endpoints reached by patients in the
2 treatment groups of ATHENA
These data show the statistical superiority of MULTAQ over placebo for the composite primary endpoint; CV hospitalizations accounted for the large majority of primary endpoint events
Approximately half of CV hospitalizations in both treatment groups were related to AF

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

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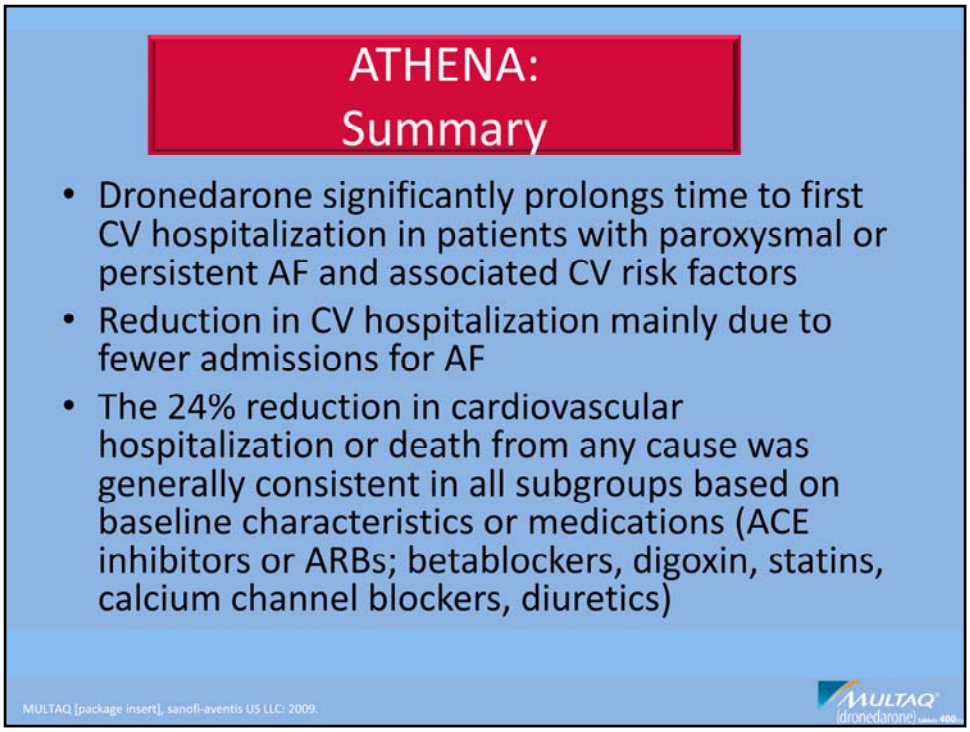


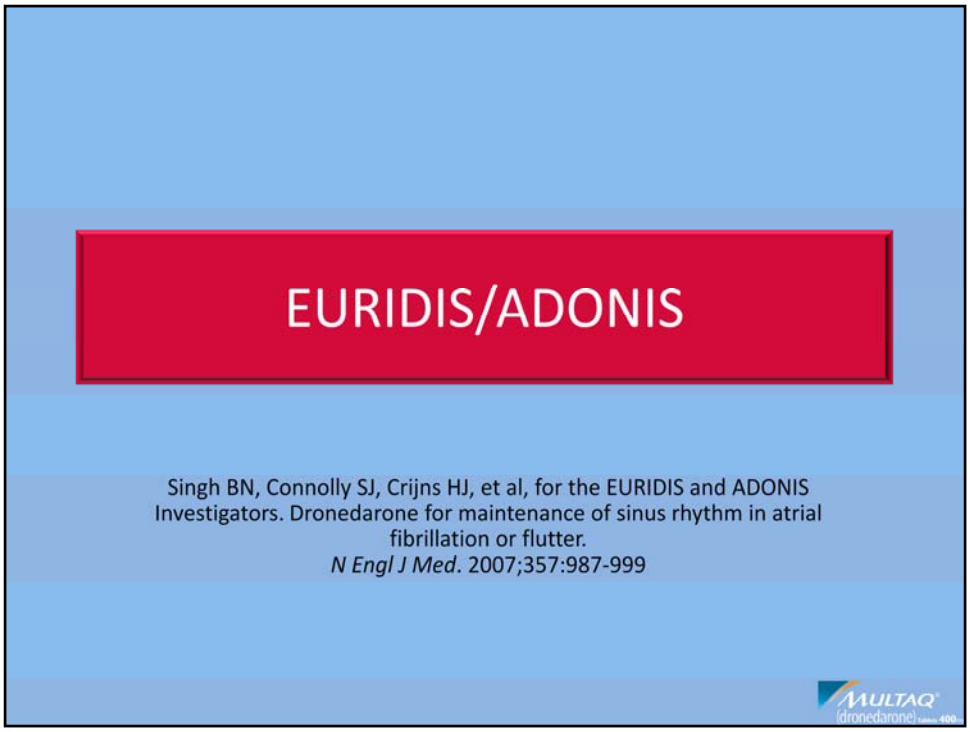

In ATHENA, MULTAQ demonstrated:

A reduced, combined endpoint of CV hospitalization or death from any cause by 24.2% when compared to placebo

Reduction in CV hospitalization mainly due to fewer admissions for AF

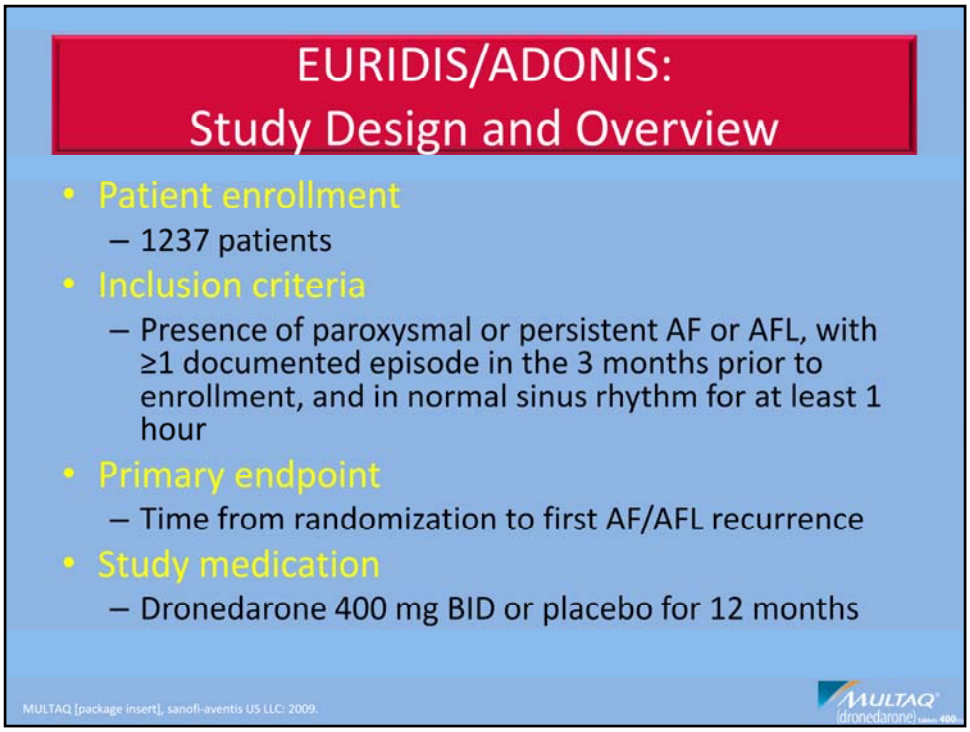
The 24% reduction in cardiovascular hospitalization or death from any cause was generally consistent in all subgroups based on baseline characteristics or medications (ACE inhibitors or ARBs; betablockers, digoxin, statins, calcium channel blockers, diuretics)

1. MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.
2. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. *J Cardiovasc Electrophysiol.* 2008;19:69-73.




EURIDIS, The **Eur**opean Trial in Atrial Fibrillation or Flutter Patients Receiving **D**ronedarone for the Ma**i**ntenance of **S**inus Rhythm, and ADONIS, the **A**merican-Australian-African Trial with **D**ronedarone in Atrial Fibrillation **o**r Flutter Patients for the Mai**n**tenance of **S**inus Rhythm, were 2 identical, placebo-controlled, multicenter, double-blind, parallel-group phase 3 trials EURIDIS was conducted in 12 European countries, and ADONIS was conducted in the United States, Canada, Australia, South Africa, and Argentina

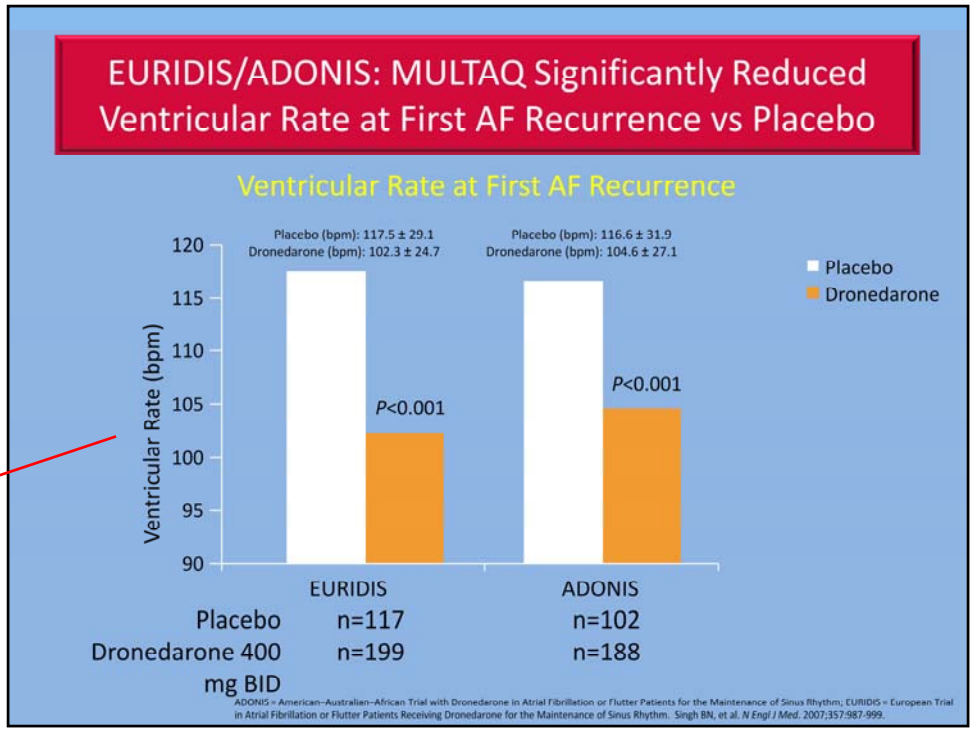
Singh BN, Connolly SJ, Crijns HJ, et al, for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987-999.




In EURIDIS and ADONIS, a total of 1237 patients in sinus rhythm with a prior episode of AF or AFL were randomized in an outpatient setting and treated with either MULTAQ 400 mg twice daily (n=828) or placebo (n=409) on top of conventional therapies (including oral anticoagulants, beta-blockers, ACE inhibitors or ARBs, chronic antiplatelet agents, diuretics, statins, digoxin, and calcium channel blockers)
Patients had at least 1 ECG-documented AF/AFL episode during the 3 months prior to study entry but were in sinus rhythm for at least 1 hour
Patients ranged in age from 20 to 88 years, with the majority being Caucasian (97%) and male (70%)
The most common comorbidities were hypertension (56.8%) and structural heart disease (41.5%), including coronary heart disease (21.8%)
Patients were followed for 12 months
Primary endpoint was time from randomization to first AF/AFL recurrence

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

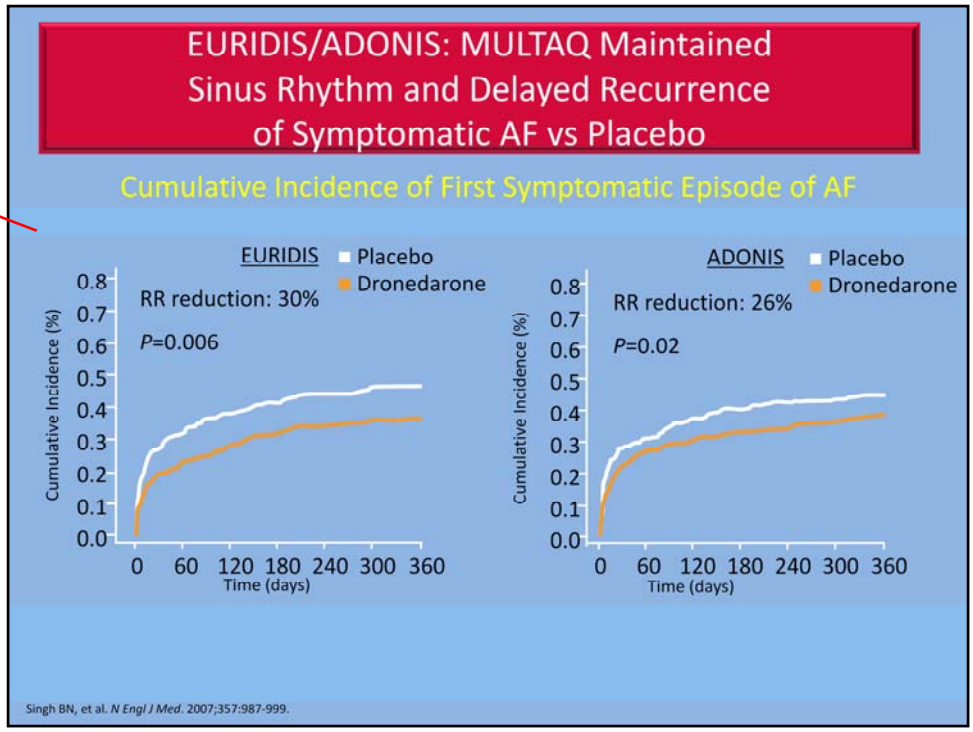
Adapted from Singh, N Engl J Med, Sept 2007, p 994/Table 2 and p 990/col 2/ lines 31-42




In addition to being consistently effective in maintaining sinus rhythm, compared with placebo, MULTAQ significantly decreased the ventricular rate during the first recurrence of atrial fibrillation/atrial flutter. **(Singh, N Engl J Med, Sept 2007, p990/col 2/lines 31-42 and p995/col 1/para1/lines 8-10)**

Singh BN, Connolly SJ, Crijns HJ, et al; for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987-999.

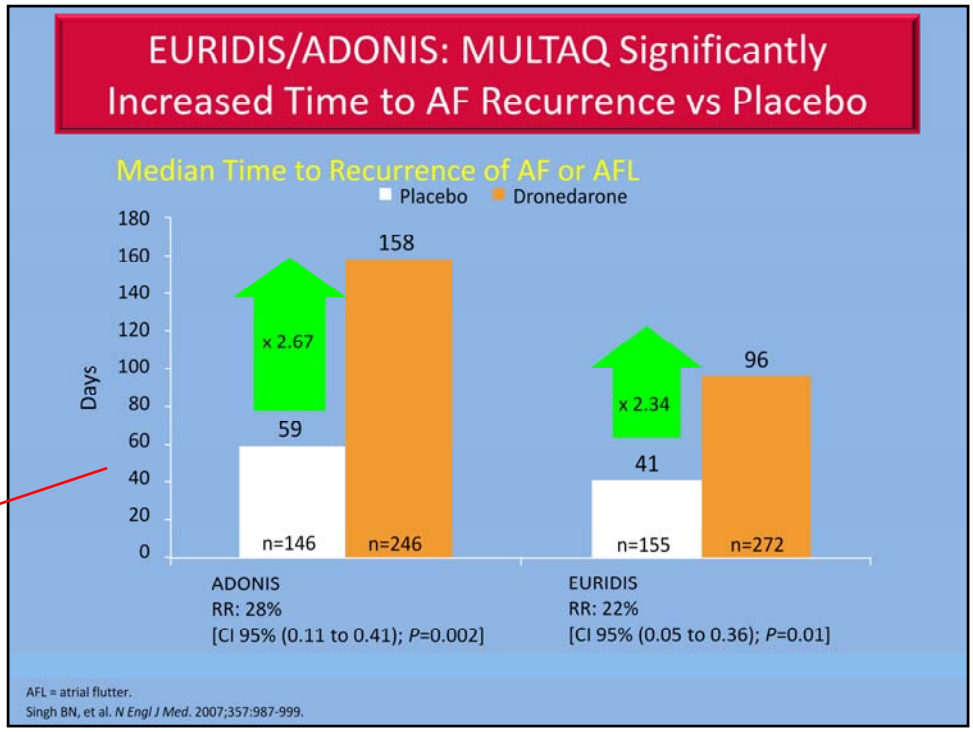
Singh, N Engl J Med, Sept 2007, p995/fig 2/A & B




As shown here, MULTAQ, compared with placebo, demonstrated a significant reduction in the cumulative incidence of a first symptomatic episode of atrial fibrillation in both EURIDIS and ADONIS. **(Singh, N Engl J Med/ Sept 2007/p 990/col 2/lines 6-16)**

Over the course of 1 year, MULTAQ showed a 30% relative risk reduction (*P*=0.006) in EURIDIS and a 26% relative risk reduction (*P*=0.02) in ADONIS. **(Singh, N Engl J Med/ Sept 2007/p 995/col 1/ para 2/lines 17-20)**

Singh BN, Connolly SJ, Crijns HJ, et al; for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987-999.




Adapted from Singh, N Engl J Med, Sept 2007, p 994/Table 2

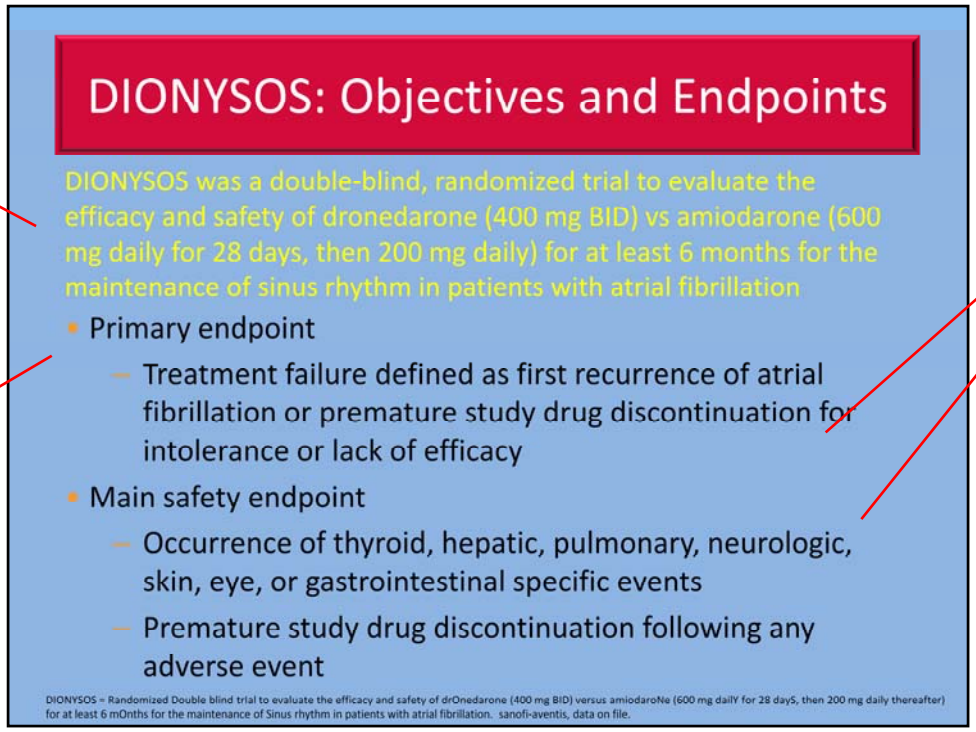
The results from EURIDIS/ADONIS demonstrated that MULTAQ prolonged the time to recurrence by a factor of more than 2, compared with placebo. **(Singh, N Engl J Med/p995/col1/para2/lines1-4)**

Singh BN, Connolly SJ, Crijns HJ, et al; for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987-999.

sanofi-aventis data on file, press release/December 2008/lines 1-7

sanofi-aventis data on file, press release/December 2008/p.1/lines 8-12

sanofi-aventis data on file, press release/December 2008/p.1/lines 14-16



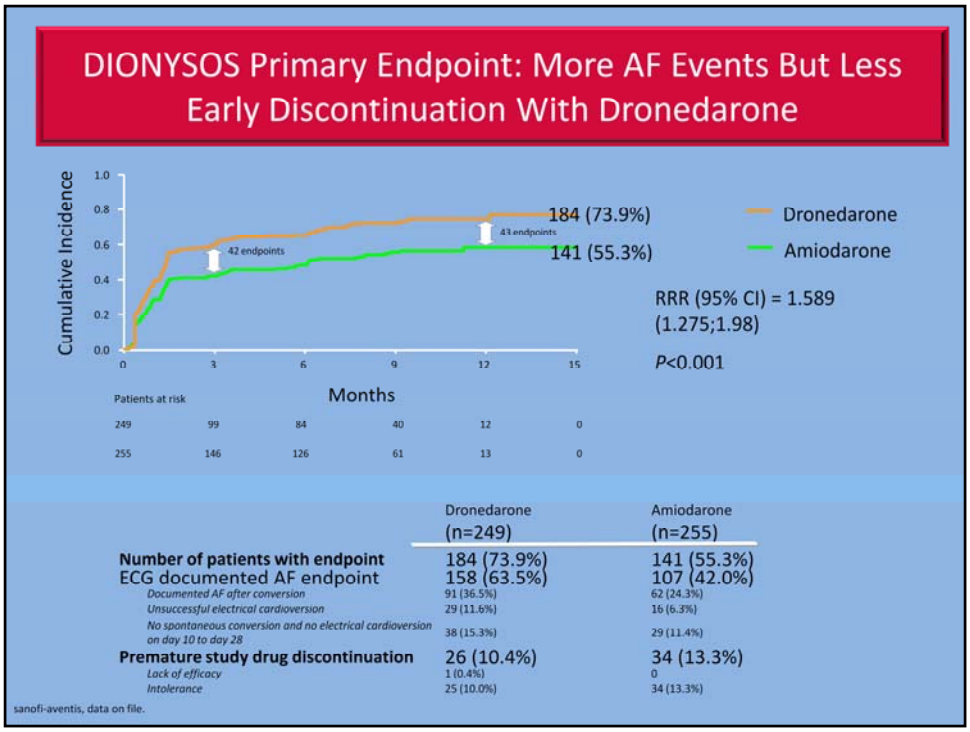

The Randomized **D**ouble blind tr**I**al to evaluate the efficacy and safety of dr**O**nedarone (400 mg BID) versus amiodaro**N**e (600 mg dail**Y** for 28 day**S**, then 200 mg daily thereafter) for at least 6 m**O**nths for the maintenance of **S**inus rhythm in patients with atrial fibrillation (DIONYSOS) was conducted to evaluate the efficacy and safety of MULTAQ vs amiodarone for the maintenance of sinus rhythm in 504 patients with persistent atrial fibrillation for a treatment duration of at least 6 months (mean follow-up of 7 months). **(sanofi-aventis data on file, press release/December 2008/lines 1-7)**

The DIONYSOS study had 2 objectives and 2 endpoints:

- The primary objective was to demonstrate that MULTAQ is superior to amiodarone in the maintenance of sinus rhythm after electrical or spontaneous conversion of persistent atrial fibrillation. The secondary objective was to evaluate the safety of MULTAQ compared with that of amiodarone. **(sanofi-aventis data on file, press release/December 2008/p.1/lines 10-11)**
- DIONYSOS had a primary endpoint of treatment failure. This was defined as the first recurrence of atrial fibrillation or premature discontinuation of study drug for intolerance or inefficacy. **(sanofi-aventis data on file, press release/December 2008/p.1/lines 9-12)**
- The other main endpoint of DIONYSOS was safety, specifically, the occurrence of thyroid, hepatic, pulmonary, neurologic, dermatologic, ophthalmologic, or gastrointestinal adverse events or premature discontinuation of the study drug due to adverse events. **(sanofi-aventis data on file, press release/December 2008/p.1/lines 14-16)**

sanofi-aventis, data on file.

Adapted from sanofi-aventis data on file, press release/December 2008/p.1/lines 8-12




The primary endpoint of DIONYSOS was defined as ECG-documented atrial fibrillation recurrence or premature study drug discontinuation for intolerance or lack of efficacy. **(sanofi-aventis data on file, press release/December 2008/p2/lines15-16)**

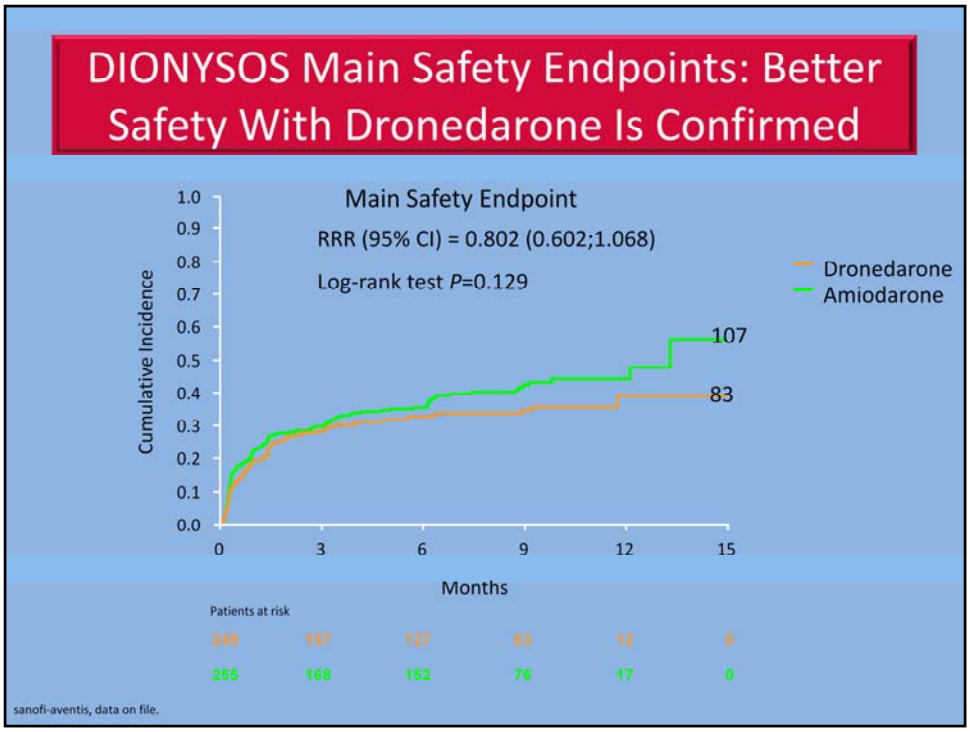
This slide shows that of 249 patients who had received dronedarone, 73.9% (184) reached the primary endpoint, compared with 55.3% (141) of the 255 patients who were receiving amiodarone (*P*<0.001). **(sanofi-aventis data on file, press release/December 2008/p1/lines8-10)**

However, it should be noted that in all patients who reached the primary endpoint, there was greater atrial fibrillation recurrence with dronedarone (36.5% vs 24.3% with amiodarone) but less early discontinuation. **(sanofi-aventis data on file, press release/December 2008/p1/line 10)**

In other words, more patients receiving amiodarone discontinued the drug prematurely than patients receiving dronedarone. **(sanofi-aventis data on file, press release/December 2008/p1/lines 11-12)**

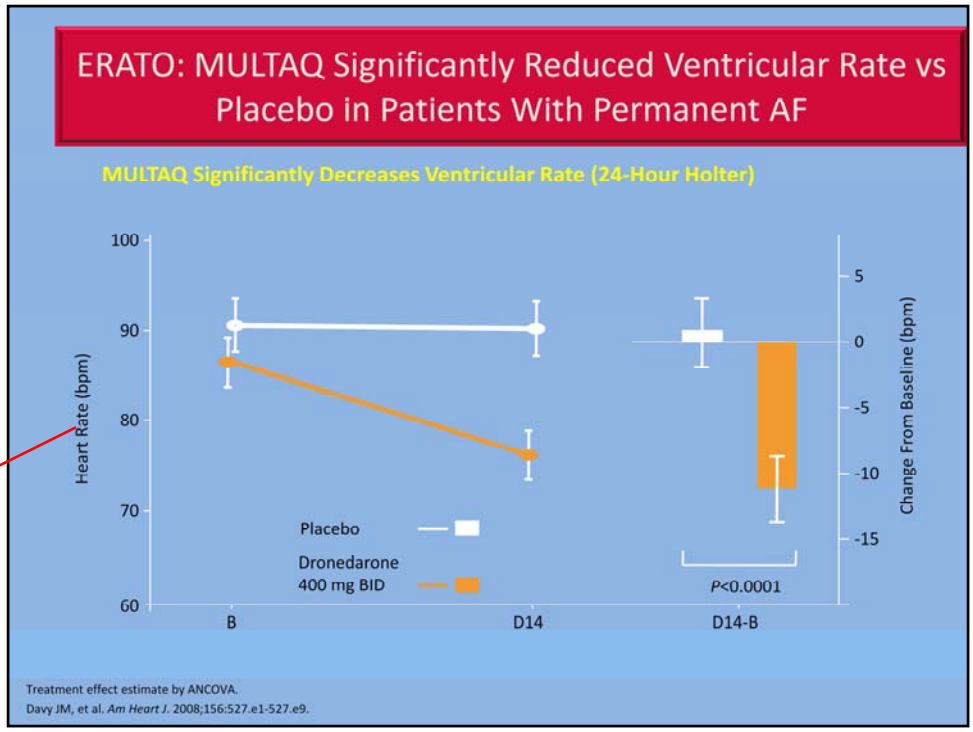
sanofi-aventis, data on file.

Adapted from sanofi-aventis data on file, press release/December 2008/p.1/lines 14-24




In DIONYSOS, the main safety endpoint confirmed that dronedarone has a better safety profile than amiodarone. **(sanofi-aventis data on file, press release/December 2008/p1/lines 13-16)**

sanofi-aventis, data on file.



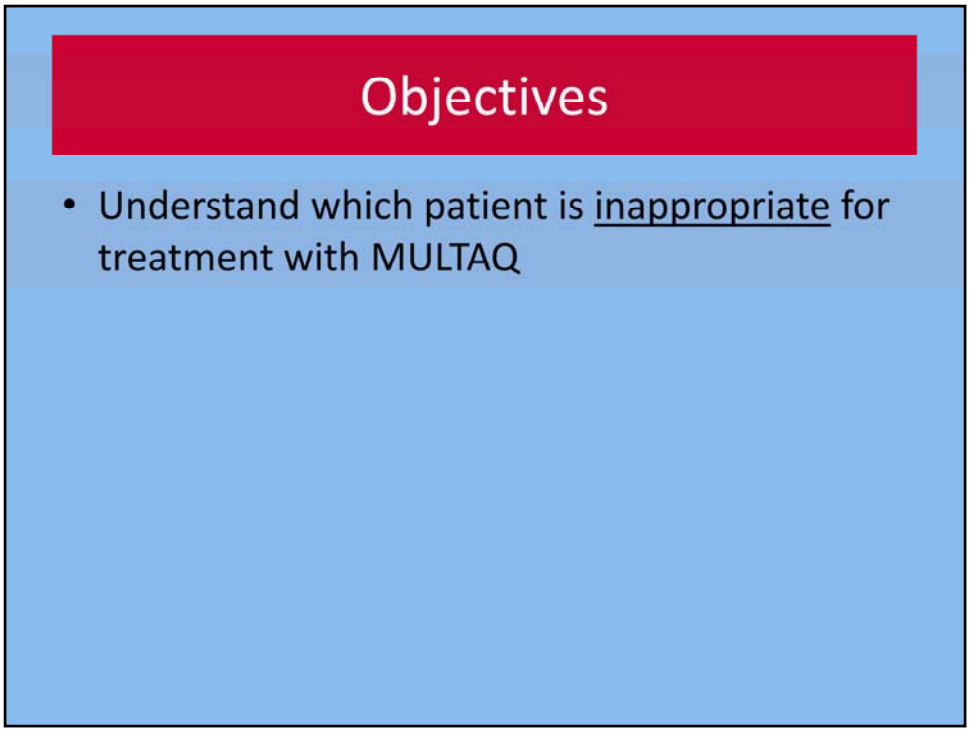

Davy, Am Heart J/Sept 2008/ p527.e6/fig 3

ERATO (**E**fficacy and safety of d**R**oned**A**rone for **T**he c**O**ntrol of ventricular rate during atrial fibrillation) was a randomized, double-blind, placebo-controlled study. There were 85 patients who received MULTAQ and 89 patients who received placebo. **(Davy, Am Heart J/Sept 2008/ p527.e1/lines A5-A10)**

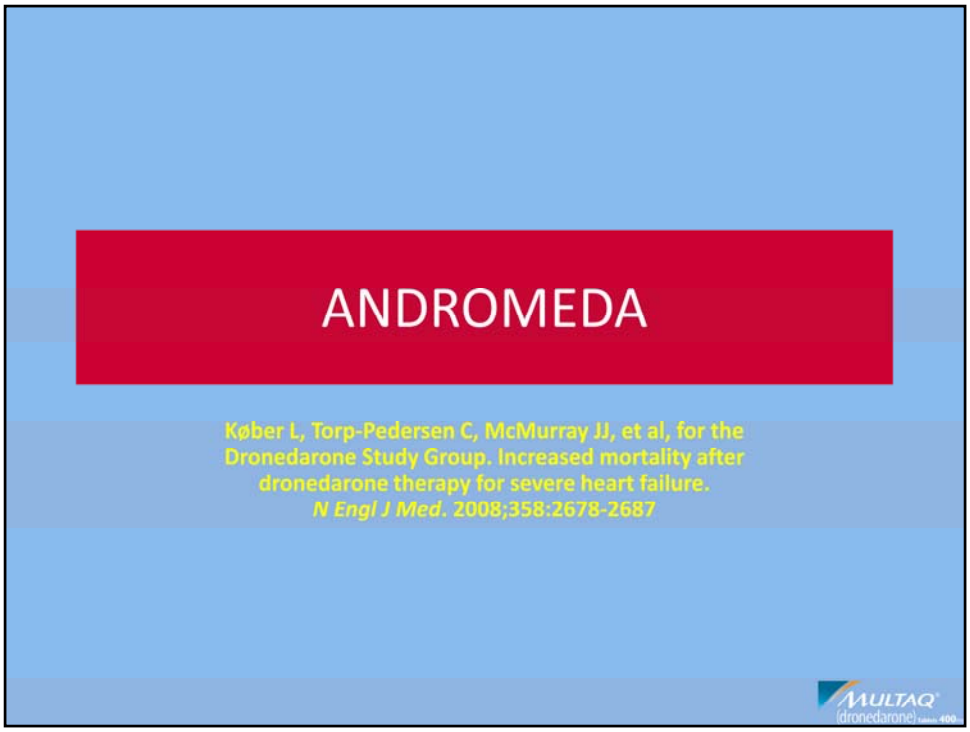
As shown here, the primary endpoint of ERATO, reduction in the resting heart rate with MULTAQ vs placebo, was achieved. **(Davy, Am Heart J/Sept 2008/ p527.e5/col 1/lines 12-15)**

- 24-hour Holter assessment showed that MULTAQ significantly decreased the mean 24-hour ventricular rate in patients with symptomatic permanent atrial fibrillation. **(Davy, Am Heart J/Sept 2008/ p527.e1/lines A10-A15 and p527.e5/col 1/lines 12-20)**
- Within 14 days of randomization, the mean ventricular rate was 90.2 beats per minute (bpm) with placebo and 76.2 bpm with MULTAQ, a highly statistically significant decrease of approximately 14 bpm ($P$<0.0001). **(Davy, Am Heart J/Sept 2008/ p527.e5/col 1/lines 12-20)**

Davy JM, Herold M, Hoglund C, et al; for the ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J*. 2008;156:527.e1-527.e9.

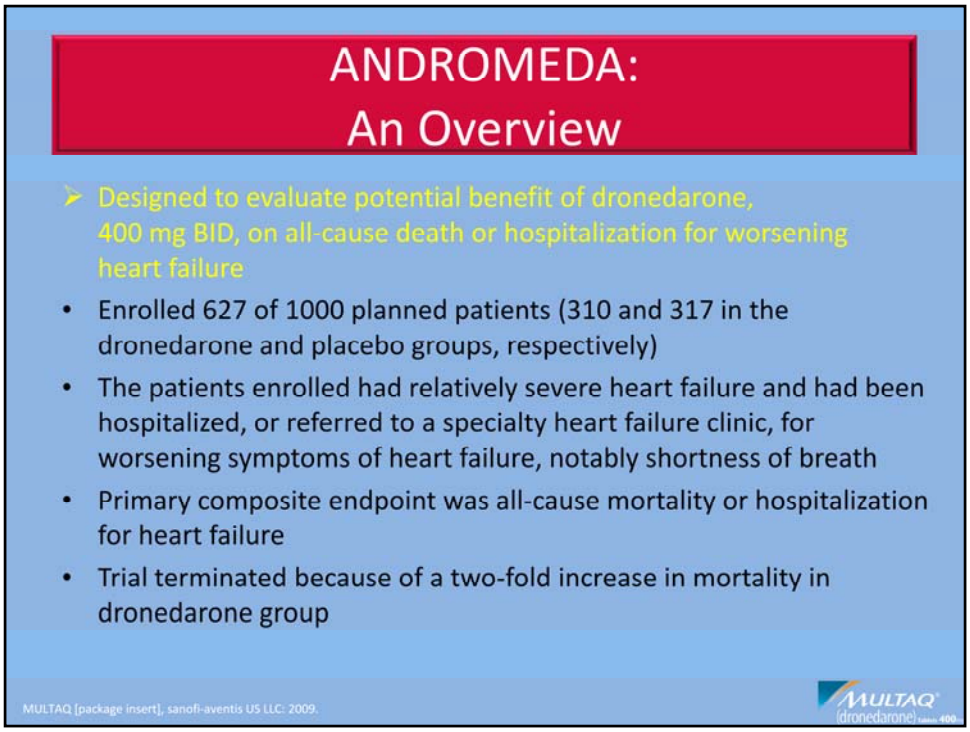



The objectives for this presentation are as follows:
To review the current state of atrial fibrillation
To present clinical data on MULTAQ and to understand the inappropriate and appropriate patient selection for treatment with MULTAQ




ANDROMEDA is the acronym for the **AN**tiarrhythmic trial with **DR**onedarone in **M**oderate to severe CHF **E**valuating morbidity **D**ecre**A**se. This was a European phase 3, multicenter, double-blind, randomized trial comparing oral dronedarone 400 mg twice daily with matching placebo in patients with severe heart failure

Køber L, Torp-Pedersen C, McMurray JJ, et al, for the Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med.* 2008;358:2678-2687.

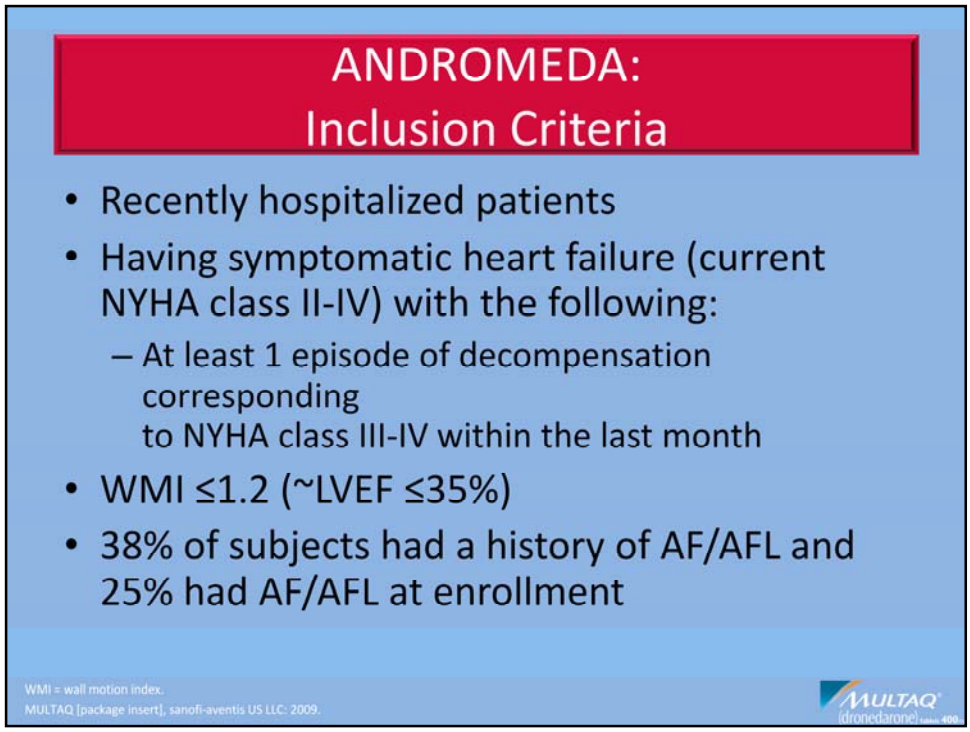



In ANDROMEDA, patients recently hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction (wall motion index ≤1.2) were randomized to either MULTAQ 400 mg twice daily or matching placebo, with a primary composite endpoint of all-cause mortality or hospitalization for heart failure

After enrollment of 627 of 1000 planned patients (310 and 317 in the dronedarone and placebo groups, respectively) and a median follow-up of 63 days, the trial was ended by the Data Safety Monitoring Board (DSMB) because of a greater than two-fold increase in mortality in the dronedarone group

The trial was ended by the DSMB on January 16, 2003, 7 months after the study began (on June 2002). Follow-up was continued until at least 6 months after withdrawal of the study drug

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.



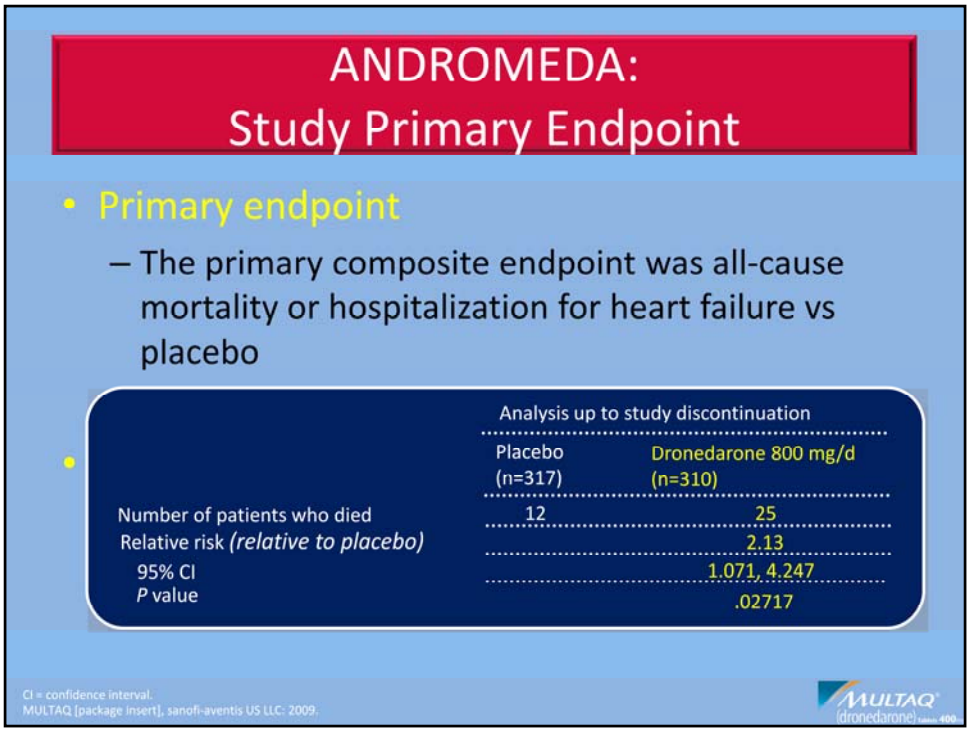

The study planned to enroll 1000 patients with high-risk or severe congestive heart failure and left ventricular systolic dysfunction (wall motion index ≤1.2) and recent acute decompensation (NYHA class III-IV)[1]

Approximately half of the study subjects had previous myocardial infarction, 63% to 67% had ischemic heart disease, 34% to 40% hypertension, 26% to 33% dilated cardiomyopathy, and 37% to 40% AF/AFL. About 30% of subjects were taking digoxin and 30% were taking anticoagulants. The large majority of subjects (84% to 88%) were taking angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs); 60% to 61% were receiving beta-blockers[2]

38% of subjects had a history of AF/AFL and 25% had AF/AFL at enrollment

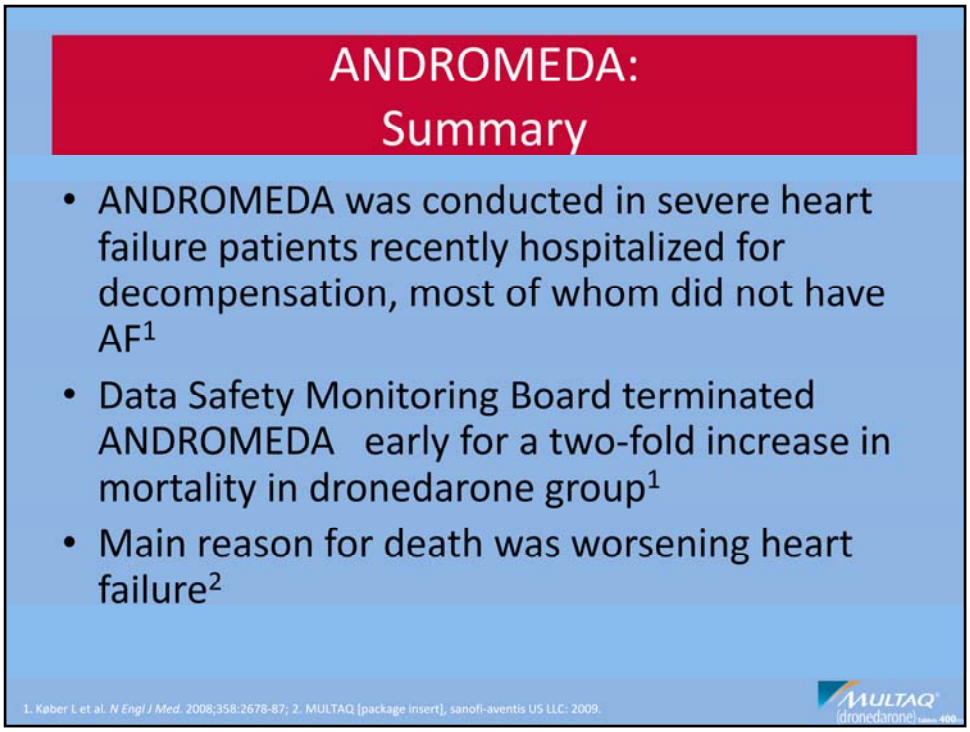
Patients were seen on day 5 (± 2 days) after randomization and again after 1 and 3 months. Subsequent visits were scheduled every 3 months[2]

1. MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.
2. Køber L, Torp-Pedersen C, McMurray JJ, et al, for the Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358:2678-2687.




The primary endpoint in the ANDROMEDA trial was the composite of death from any cause or hospitalization for worsening heart failure

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.




In the ANDROMEDA trial, dronedarone did not reduce mortality or decrease CV hospitalizations compared to placebo in patients with advanced heart failure; most of these heart failure patients (60% to 63%) did not have AF/AFL[1]
ANDROMEDA was terminated early for safety reasons[1]
The main reason for death was worsening heart failure[1]
No significant difference in arrhythmic events and sudden deaths was seen between the placebo and dronedarone groups[1]

1. Køber L, Torp-Pedersen C, McMurray JJ, et al, for the Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358:2678-2687.
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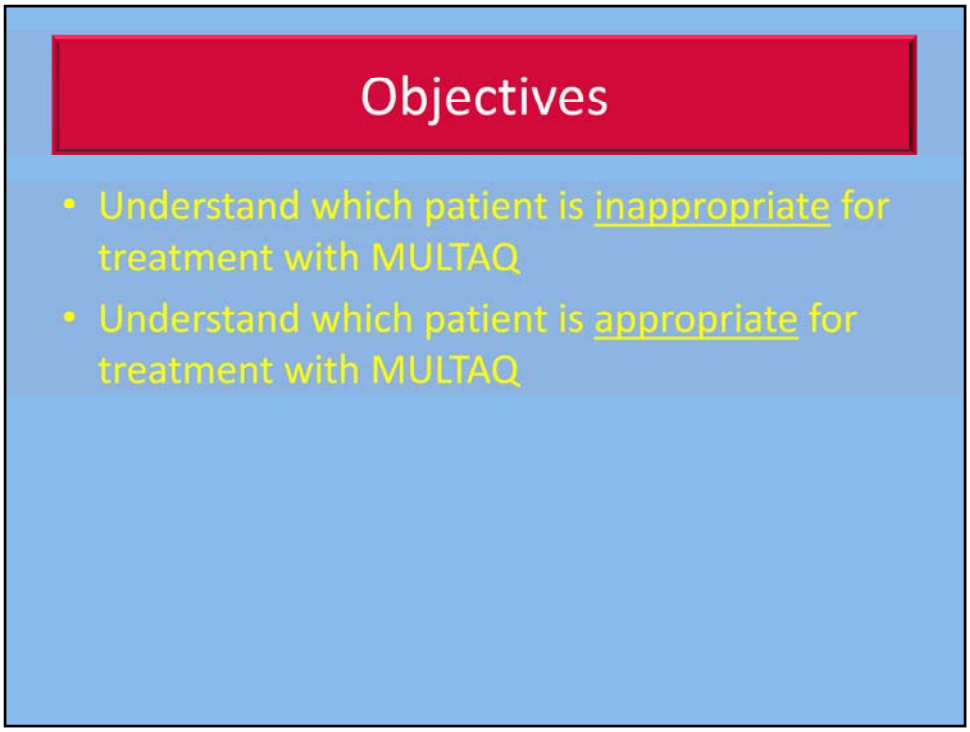


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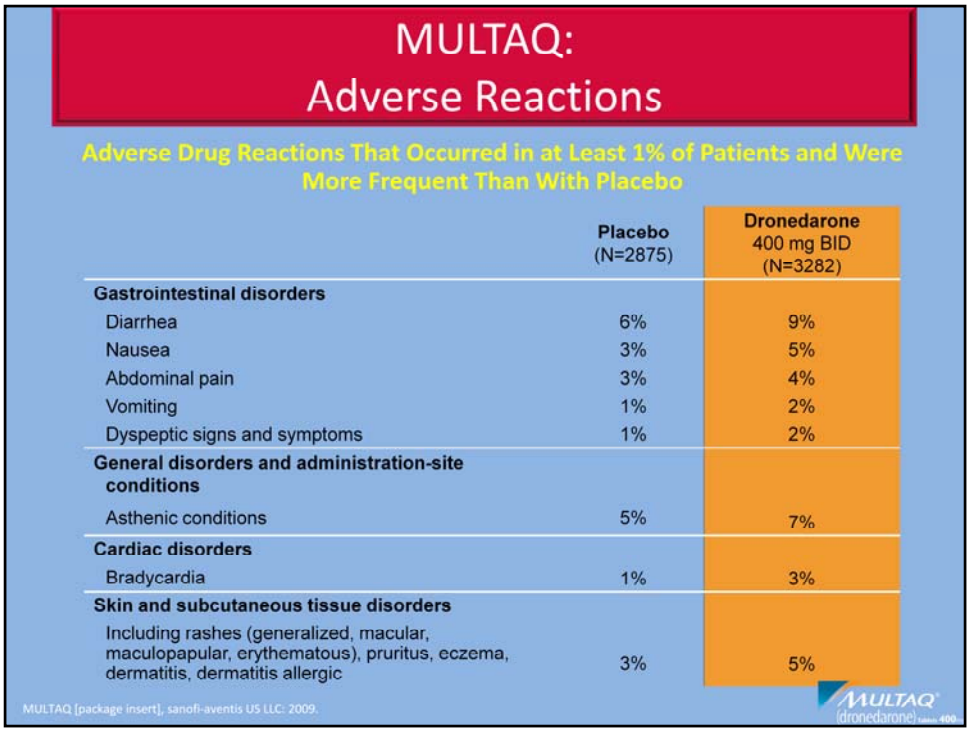



This slide summarizes the most common adverse reactions (occurring in more than 1% of patients) across 5 different clinical trials: ATHENA, EURIDIS/ADONIS, ERATO, and DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion)

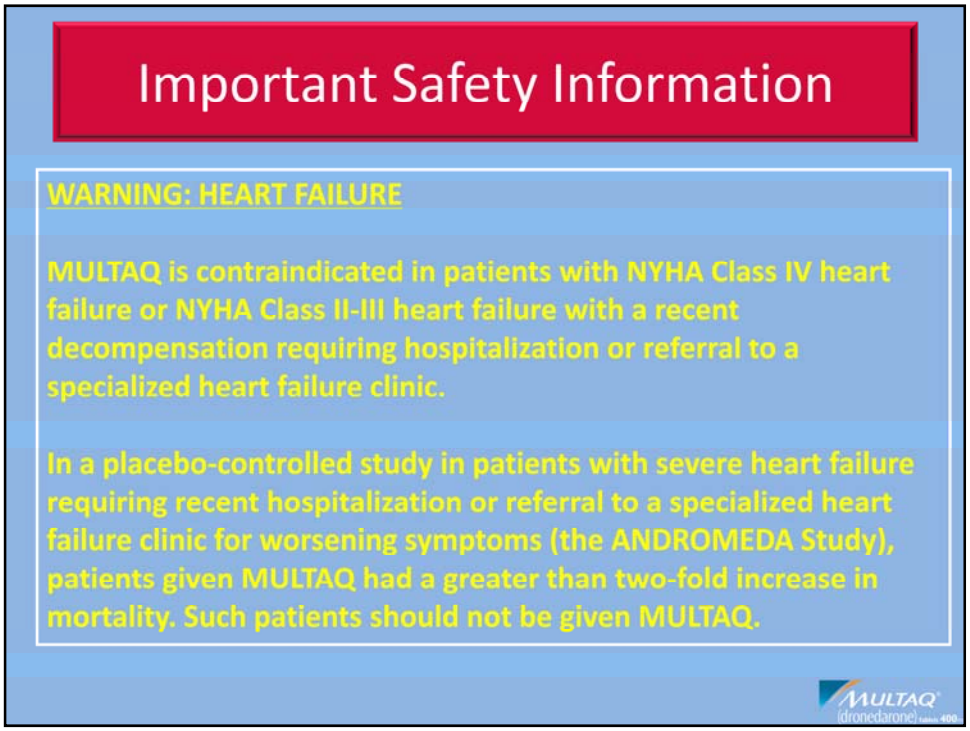
In these clinical trials, the most frequent adverse reactions observed with MULTAQ 400 mg twice daily were diarrhea, nausea, abdominal pain, vomiting, dyspepsia, and asthenia

Premature discontinuation due to adverse reactions occurred in 11.8% of patients receiving MULTAQ and 7.7% of the placebo-treated group

The most common reasons for discontinuation of therapy with MULTAQ compared to placebo were gastrointestinal disorders (3.2% vs 1.8%, respectively) and QT prolongation (1.5% vs 0.5%, respectively)

In healthy subjects, MULTAQ administered at a dose of 600 mg twice daily increased S-warfarin by 1.2-fold, with no change in R-warfarin and no clinically significant increase in the international normalized ratio (INR)

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.




The boxed warning in the Important Safety Information for use of MULTAQ is as follows

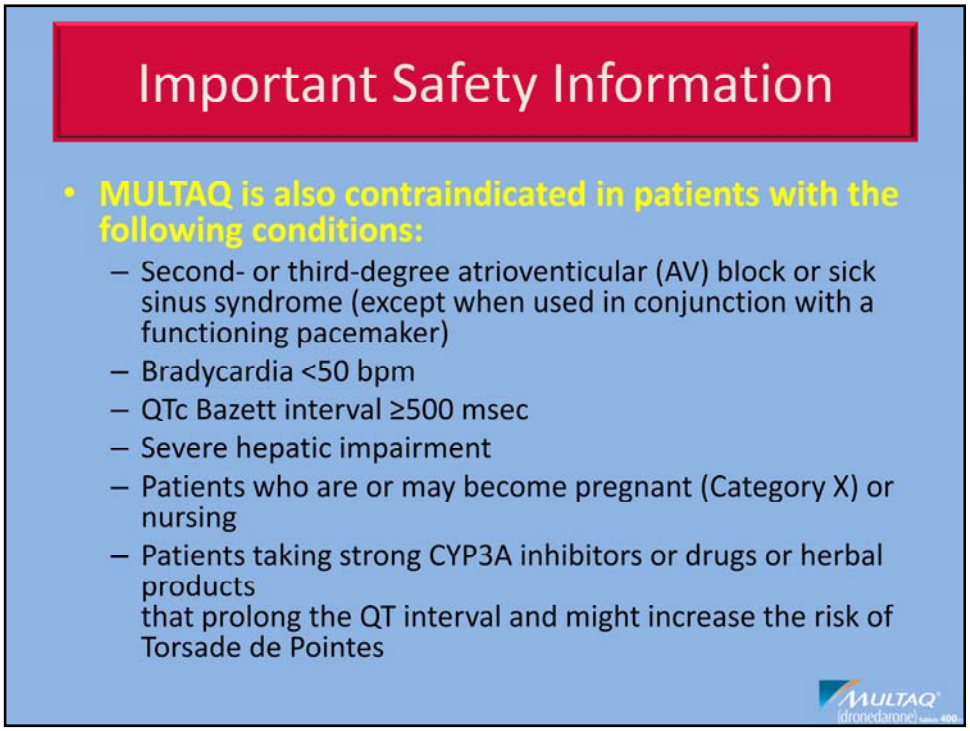
MULTAQ is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.
In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given MULTAQ had a greater than two-fold increase in mortality. Such patients should not be given MULTAQ.

Additional Important Safety Information states MULTAQ contraindicated in the following patients and conditions:

MULTAQ is also contraindicated in patients with the following conditions:

- Second- or third-degree atrioventicular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm
- QTc Bazett interval ≥500 msec
- Severe hepatic impairment
- Patients who are or may become pregnant (Category X) or nursing
- Patients taking strong CYP3A inhibitors or drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

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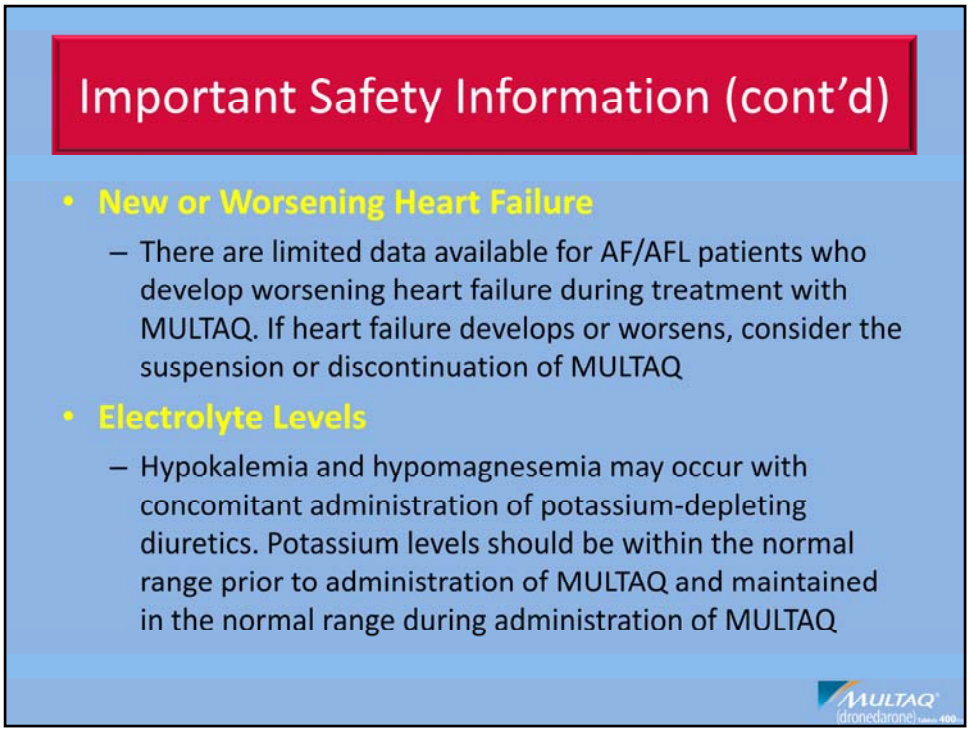



In patients with New or worsening Heart Failure it is important to note that:

There are limited data available for AF/AFL patients who develop worsening heart failure during treatment with MULTAQ. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ

With regards to Electrolyte levels the HCP should be aware that:

Hypokalemia and hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ

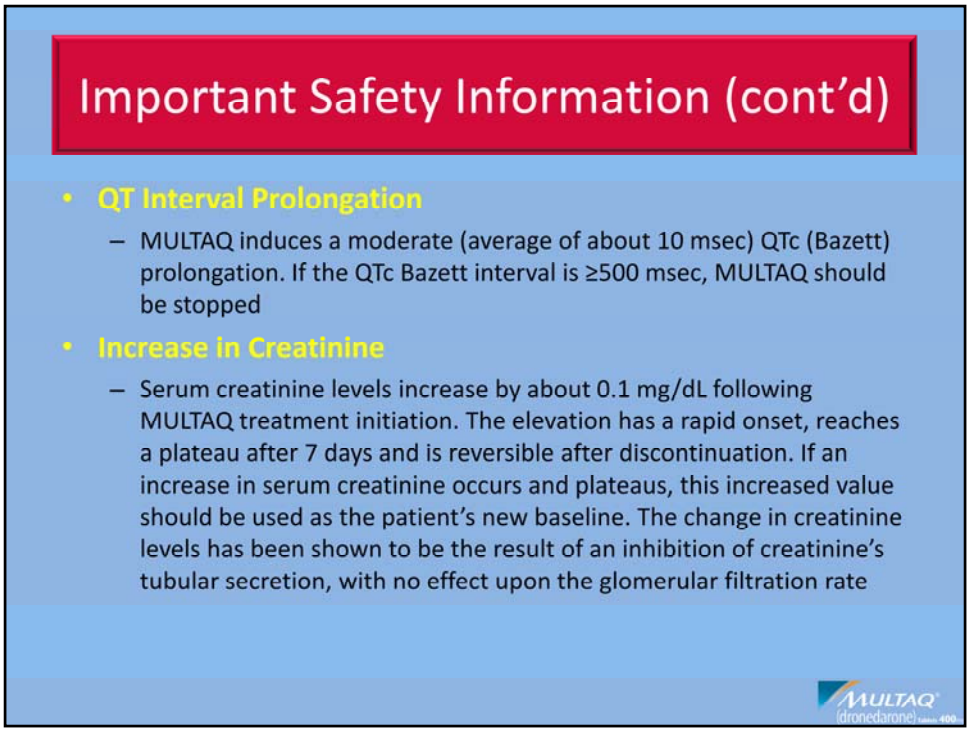
With regard to the issue of prolonging of the QT interval:

MULTAQ induces a moderate (average of about 10 msec) QTc (Bazett) prolongation. If the QTc Bazett interval is ≥500 msec, MULTAQ should be stopped

With regard to Serum Creatinine Increases:

Serum creatinine levels increase by about 0.1 mg/dL following MULTAQ treatment initiation. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. If an increase in serum creatinine occurs and plateaus, this increased value should be used as the patient's new baseline. The change in creatinine levels has been shown to be the result of an inhibition of creatinine's tubular secretion, with no effect upon the glomerular filtration rate

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

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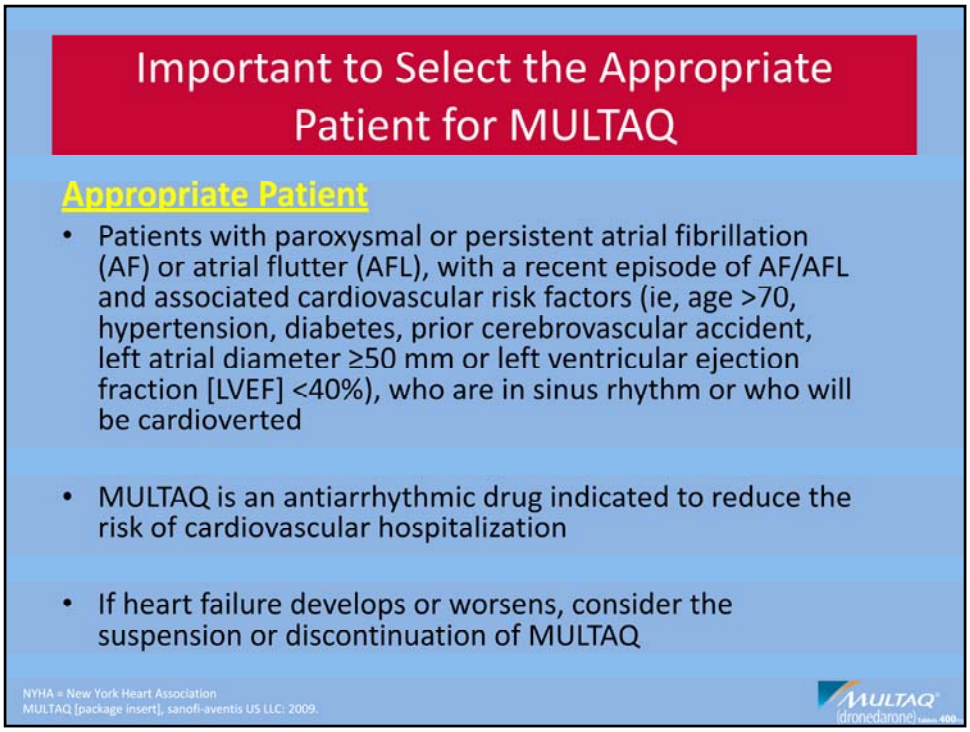
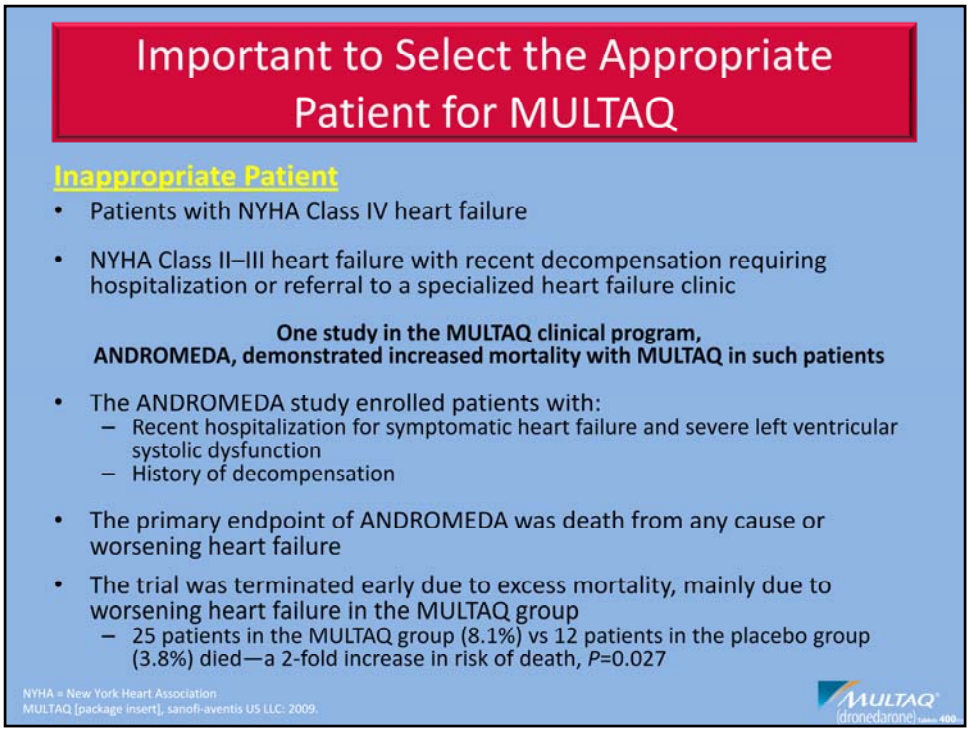



As we learned from the ATHENA trial, the appropriate patient is a patient with paroxysmal or persistent AF or AFL with a recent episode of AF/AFL and associated CV risk factors (ie, age >70, hypertension, diabetes, prior cerebrovascular accident) with left atrial diameter ≥50 mm or LVEF <40% in sinus rhythm or who will be cardioverted.

As was learned from the ANDROMEDA trial, the inappropriate patient is a patient with:

- NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic
- Recent hospitalization for symptomatic heart failure and severe left ventricular systolic dysfunction
- History of decompensation

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

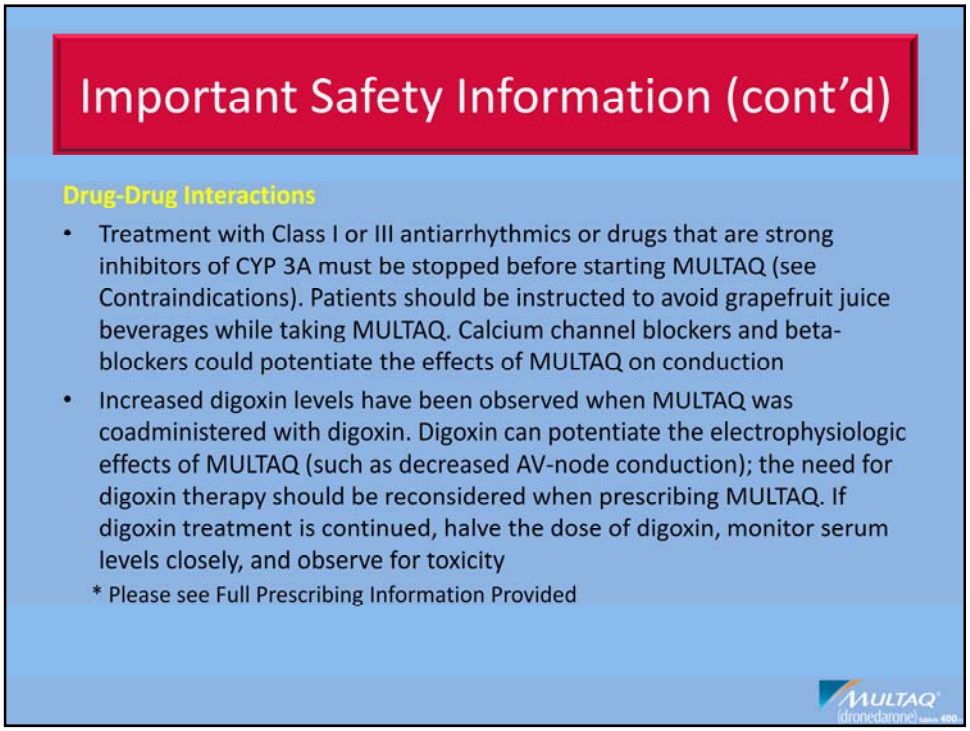



As we learned from the ATHENA trial, the appropriate patient is a patient with paroxysmal or persistent AF or AFL with a recent episode of AF/AFL and associated CV risk factors (ie, age >70, hypertension, diabetes, prior cerebrovascular accident) with left atrial diameter ≥50 mm or LVEF <40% in sinus rhythm or who will be cardioverted.

As was learned from the ANDROMEDA trial, the inappropriate patient is a patient with:

- NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic
- Recent hospitalization for symptomatic heart failure and severe left ventricular systolic dysfunction
- History of decompensation

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.



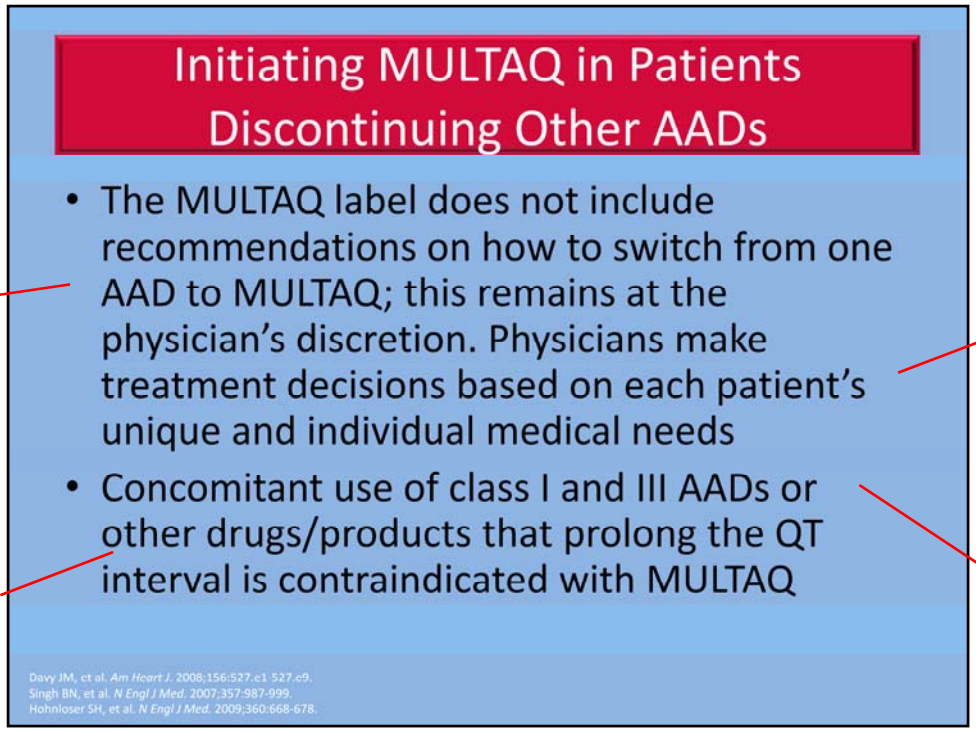

Use of MULTAQ with other Class II or III antiarrythmic drugs (AADs) or concurrently with strong CYP3A inhibitors

Must be stopped before starting MULTAQ. Patients should be instructed to avoid grapefruit juice beverages while taking MULTAQ. Calcium channel blockers and beta-blockers could potentiate the effects of MULTAQ on conduction

With regard to MULTAQ and Digoxin:

Increased digoxin levels have been observed when MULTAQ was coadministered with digoxin. Digoxin can potentiate the electrophysiologic effects of MULTAQ (such as decreased AV-node conduction); the need for digoxin therapy should be reconsidered when prescribing MULTAQ. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.




MULTAQ PI p6/lines 156-158

Davy, Am Heart Journal, Sept2008/p572e2/col2/para5/lines34-36

Hohnloser, N Engl J Med. 2009/p670/c1/lines 28-30

Singh, N Engl J Med Sept 2007/p988/col2/lines 39-41

The MULTAQ clinical trials ERATO, EURIDIS/ADONIS, and ATHENA had specific AAD exclusion criteria for atrial fibrillation patients enrolling in these studies:

Patients enrolled in ERATO underwent a 2-month prior washout from amiodarone.[1] **(Davy, Am Heart Journal, Sept2008/p572e2/col2/para5/lines34-36)**

Patients in EURIDIS/ADONIS were permitted to have had previous treatment with amiodarone and could be enrolled immediately after discontinuation.[2] **(Singh, N Engl J Med Sept 2007/p988/col2/lines 39-41)**

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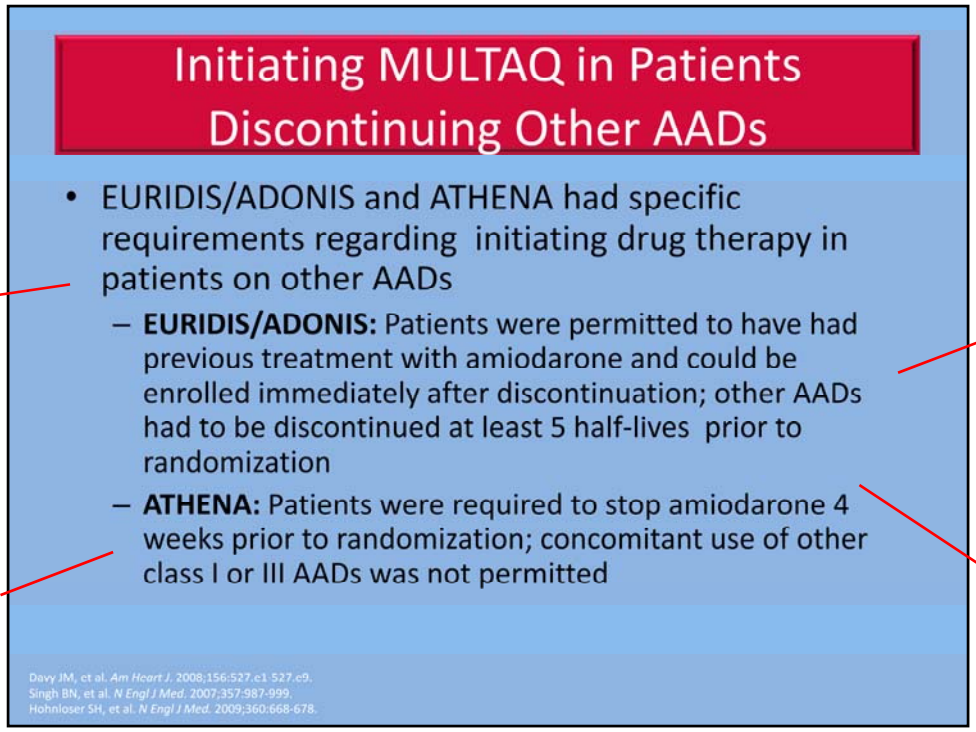
1. Davy JM, Herold M, Hoglund C, et al; for the ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J*. 2008;156:527.e1-527.e9.
2. Singh BN, Connolly SJ, Crijns HJ, et al; for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987-999.
3. Hohnloser SH, Crijns HJ, van Eickels M, et al; for the ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360:668-678.

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