

MULTAQ Indication and Boxed Warning

To reduce the risk of cardiovascular hospitalization in patients with a recent episode of paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), who are in sinus rhythm or who will be cardioverted, and have at least one of the following CV risk factors:

- Age >70 y
- Hypertension
- Diabetes
- Prior cerebrovascular accident
- Left atrial diameter \geq 50 mm
- LVEF <40%

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 the ANDROMEDA Study, a greater than two-fold increase in mortality was observed in this unstable population.

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

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VOICE OVER SCRIPT:

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter, with a recent episode of atrial fibrillation or atrial flutter, and associated cardiovascular risk factors (i.e., age > 70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter \geq 50 mm or left ventricular ejection fraction < 40%), who are in sinus rhythm or who will be cardioverted.

MULTAQ is contraindicated in patients with New York Heart Association Class IV heart failure, or New York Heart Association Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. In the ANDROMEDA Study, a greater than two-fold increase in mortality was observed in this unstable population.

MULTAQ® Clinical Trial Review

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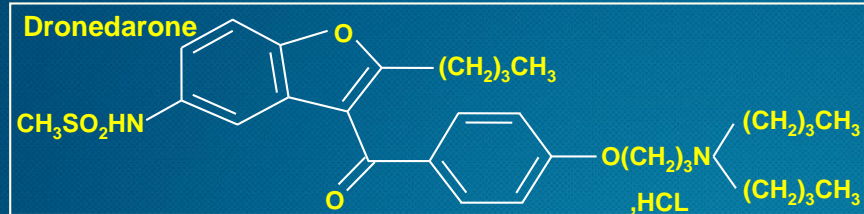
DR. PRYSTOWSKY:

So with great pleasure now, I'll come to Dr. Kowey, who is going to go through all the trials that dealt with dronedarone and MULTAQ. Thanks, Peter.

DR. KOWEY:

Thank you, Eric. First of all, thanks for including me, and putting this program together. It's a pleasure to interact with all of my distinguished colleagues. Dronedarone underwent a very extensive clinical development program over a decade and a half of clinical trials. So there is a lot of information about the drug. I think these trials really help us to understand some of the principles of where we're trying to go in the management of our patients. You asked some very important questions about outcomes, we'll be focusing on some of that information, and integrating some of the more classical designs into a discussion of where we end up with patients in terms of real benefit.

MULTAQ® (dronedarone)



• Mechanism of action¹

- Multichannel blocker
- Blocks Ca⁺⁺, Na⁺, K⁺ channels
- Possesses electrophysiologic characteristics of all 4 Vaughan-Williams classes
- Maintains action with increasing heart rates
- Reduces potential for reentry
- Low proarrhythmic potential

• Chemical structure²

- A benzofuran derivative: N-(2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl) methanesulfonamide, hydrochloride

• Pharmacokinetic properties²

- Elimination half-life is 13-19 hours
- After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment
- Extensively metabolized, mainly by CYP3A
- Bioavailability is increased by meals
- Binds mainly to albumin

1. MULTAQ [package insert]. sanofi-aventis US LLC: 2009.
2. Hodeige D, et al. *Eur J Pharmacol*. 1995;279:25-32.

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DR. KOWEY:

So just to remind everyone that we're talking about a drug that is a benzofuran derivative, a drug with multi-channel effects, as Gus talked about, effects on several different ion currents.

MULTAQ Indication

To reduce the risk of cardiovascular hospitalization in patients with a recent episode of paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), who are in sinus rhythm or who will be cardioverted, and have at least one of the following CV risk factors:

- Age >70 y
- Hypertension
- Diabetes
- Prior cerebrovascular accident
- Left atrial diameter \geq 50 mm
- LVEF <40%

MULTAQ [package insert]. sanofi-aventis US LLC. 2009.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

I'll start off by just reminding everyone that the development program for dronedarone led us to an indication that's a bit unique. We don't think about atrial fibrillation drugs necessarily as affecting cardiovascular outcomes, but right out of the chute it's important for people to understand that based on the ATHENA results, in those patients that are enrolled in ATHENA, and the ATHENA endpoint, we'll talk about that trial in a few minutes. The labeling for this drug is such that it includes not just atrial fibrillation and its indication, but also aspects of vascular risk. So like the patients that you described, Eric, in AFFIRM, these are patients that are elderly that were studied in ATHENA, that had concomitant cardiovascular issues, and I think that's important because an increasing percentage of the patients we see with atrial fibrillation have these kinds of vascular risk issues, and in those patients, symptom relief may not be the only principle to worry about. We're also concerned with these patients feeling better, and staying out of the hospital.

MULTAQ Key Clinical Trials

Study	Design	Description
DAFNE	Dose Ranging Study	Dose Ranging Study
EURIDIS/ ADONIS	AF/AFL Maintenance N=615/629 (EU/US) 400 mg BID vs placebo (1 y)	EFFECTS ON AF CONTROL Time from randomization to first AF/AFL recurrence
ANDROMEDA	Morbidity/Mortality in HF N=627 (1000 planned; intl study) 400 mg BID vs placebo (1 y)	OUTCOMES IN SEVERE OR RECENTLY DECOMPENSATED HF <i>Study stopped early due to increased mortality in the MULTAQ arm</i>
ATHENA	Morbidity/Mortality in AF + CV Risk Factors N=4628 400 mg BID vs placebo (1 y)	CV OUTCOMES IN AF Time to first CV hospitalization or death from any cause

Patients were in sinus rhythm or to be cardioverted at enrollment in MULTAQ clinical trials.

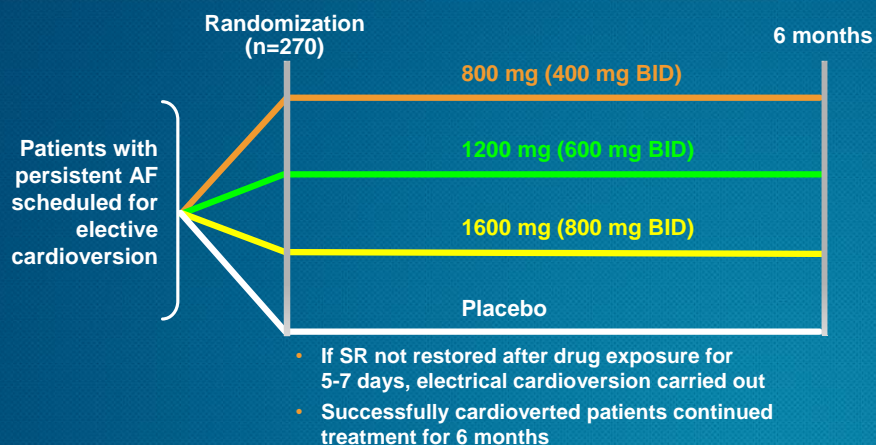
Patel C, et al. *Circulation*. 2009;120:636-644.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

As I said, there's a wealth of clinical trial experience with dronedarone. We're going to distill this down to talking about four sets of trials, and each of these trials have a point to make in terms of what clinicians need to know about the drug. So we'll start off with DAFNE.

DAFNE: MULTAQ Dose-Ranging Study



Prospective, randomized study conducted in 50 centers, 11 countries

Touboul P, et al. *Eur Heart J*. 2003;24:1481-1487.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

DAFNE was a phase two trial conducted with dronedarone in the very early days of clinical development, specifically for the purposes of picking dose. And I wanted to briefly describe this, because I'm sure Eric, and David and Gus, you all get asked questions about the dosing, because there's only a single dose, 400 milligrams twice per day. There's no up titration or down titration. That dose was actually selected based on the DAFNE experience. What DAFNE showed was that the 400 milligram twice a day dose of dronedarone was the most effective of the doses studied, and the best tolerated.

We don't have clinical trial experience at 200 milligrams twice per day. We have some earlier phase one experience that suggests that it probably isn't potent enough. But this appeared to be, the 400 milligram twice per day dose seemed to be a good compromise and was the one taken forward. So for all of the other clinical trial data I'm going to describe, all the pivotal trials, that was the dose that was utilized.

EURIDIS/ADONIS: Study Design and Overview

Objective¹

- Dronedarone vs placebo in maintaining sinus rhythm after electrical, pharmacologic, or spontaneous conversion from AF/AFL

Enrollment¹

- 1237 patients
- 2 identical, multicenter, double-blind, parallel-group trials
- EURIDIS conducted in 12 European countries
- ADONIS in US, Canada, Australia, South Africa, and Argentina

Standard background therapy was permitted including beta-blockers, CCBs, digoxin, ACE inhibitors/ARBs, statins, oral anticoagulants and aspirin^{†2}*

*CCBs restricted to those with heart rate lowering effects.

†MULTAQ may interact with several agents listed above. Please see Important Safety Information included in this presentation

CCBs = calcium channel blockers; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.

1. Singh BN, et al. *N Engl J Med.* 2007;357:987-999.

2. MULTAQ [package insert]. sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including **boxed WARNING**.

DR. KOWEY:

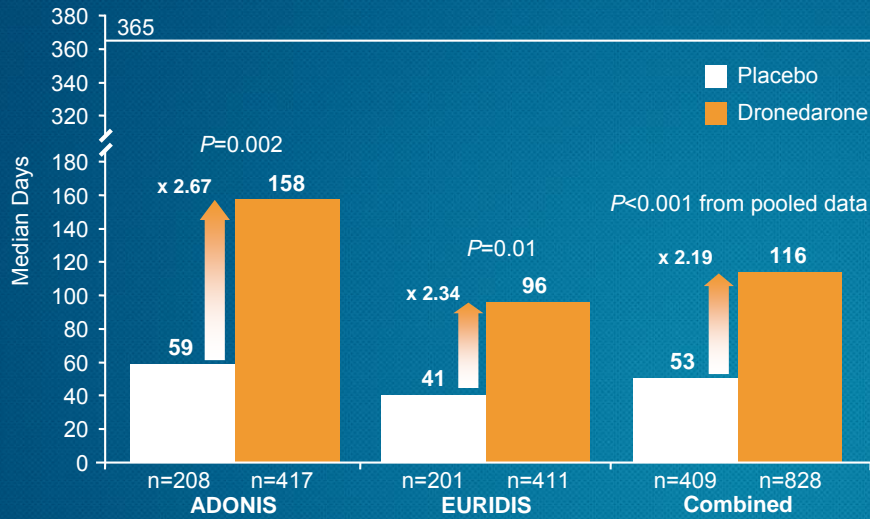
The second twin studies that I'll describe are EURIDIS and ADONIS. These studies were carried out world wide, and EURIDIS was predominantly a European trial, ADONIS in the U.S., and Australia, in South Africa, and Argentina. These were identical multi-center, double-blind, parallel studies of 400 milligrams twice per day of dronedarone, and the endpoint in this trial was the classic time to first recurrence of atrial fibrillation. This is a drug that is active in atrial fibrillation, and efficacious.

1. 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.

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

EURIDIS/ADONIS: Dronedarone Prolonged Time to First Recurrence

Primary End Point



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

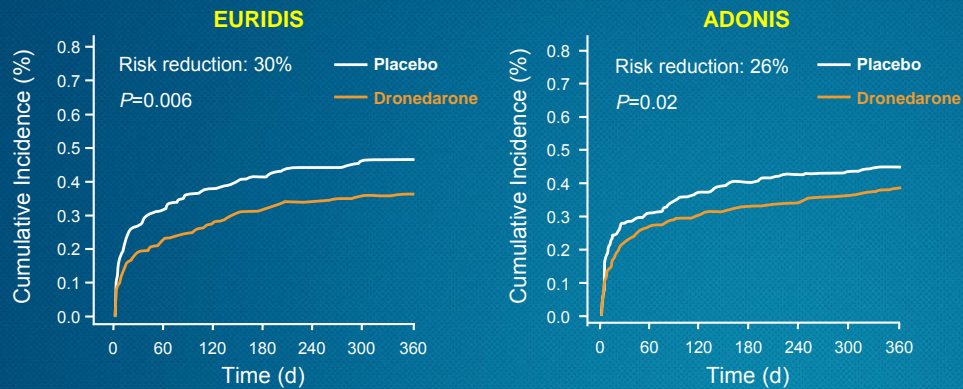
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DR. KOWEY:

This slide shows you both the results from ADONIS and EURIDIS, and then a pooled analysis. The patients, even though they came from different parts of the world, were basically the same kinds of patients, same patient descriptors. As you can see from this slide, both of the trials, as well as the pooled analysis, showed a statistically significant improvement in time to first recurrence of atrial fibrillation with patients treated with dronedarone compared to those patients treated with placebo--a fairly robust treatment effect.

EURIDIS/ADONIS: Reduced Cumulative Incidence of First Symptomatic Episode of AF

Secondary End Point



In Pooled Data, 62.3% of Dronedaronne-Treated Patients vs 54% of Patients on Placebo Were Free of Symptomatic Recurrences at 1 Year

Singh BN, et al. *N Engl J Med.* 2007;357:987-999.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

The next slide shows the secondary endpoint for EURIDIS and ADONIS, which was symptomatic episodes of atrial fibrillation, and the relative risk reductions here are somewhere between 25 and 30 percent,. And this, again, is for patients who had to manifest some symptomatic episode of atrial fibrillation.

1. Singh BN, Connolly SJ, Crijns HJ, et al, for the EURIDIS and ADONIS Investigators. Dronedaronne for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med.* 2007;357:987-999.
2. MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

EURIDIS/ADONIS: Summary

- Dronedarone prolonged time to first recurrence vs placebo during 1 year of treatment
 - Reduced risk of first recurrence by 25% ($P < 0.001$, pooled data)¹
 - Absolute difference in recurrence rate of 11% at 1 year¹
 - Majority of first recurrences were symptomatic²
- Dronedarone significantly reduced symptomatic burden of AF vs placebo at 1 year²
 - 62.3% of patients on dronedarone were free of symptomatic AF recurrence vs 54% on placebo

1. MULTAQ [package insert]. sanofi-aventis US LLC: 2009.
2. Singh BN, et al. *N Engl J Med.* 2007;357:987-99.

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DR. KOWEY:

So in summary, these two trials proved that dronedarone, at a dose of 400 milligrams twice per day, was responsible for a substantial improvement in the time to first recurrence of atrial fibrillation. The other thing that these studies showed was that there was a reduction in the symptomatic burden of the arrhythmia.

I want to remind people that EURIDIS and ADONIS enrolled not necessarily older patients, not necessarily ATHENA-like patients, but a lot of patients with atrial fibrillation across the spectrum, all the way from lone atrial fibrillation, all the way out to patients with a significant amount of cardiovascular disease.

1. 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.
2. MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.

ANDROMEDA: Study Design and Overview

Objective

- To evaluate dronedarone on all-cause death or hospitalization for worsening heart failure

Enrollment

- 627 of 1000 planned patients with median follow-up of 63 days
- Patients were predominantly NYHA class II (40%) and class III (57%)
 - 38% had history of AF/AFL (25% had AF at randomization)
 - May have been clinically improved at enrollment, and it is the history of decompensation that characterized them

Trial terminated early by DSMB due to 2-fold increase in mortality in dronedarone group.
There were also excess hospitalizations for CV reasons in the dronedarone group (71 vs 51 for placebo)

DSMB = Data Safety Monitoring Board.
MULTAQ [package insert]. sanofi-aventis US LLC: 2009.

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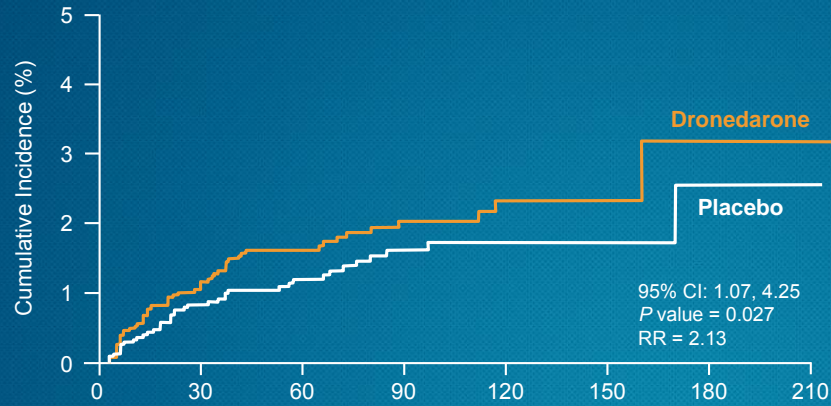
DR. KOWEY:

The third study that I'll describe is ANDROMEDA. This was not an atrial fibrillation study, this was a mortality study carried out with this drug in a fairly high risk patient population. These were patients who had recently destabilized severe heart failure, requiring either hospitalization, or a visit to a specialized clinic, patients with systolic dysfunction, low ejection fractions, and a relatively sick group of patients with heart failure.

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.

ANDROMEDA: Increased All-Cause Mortality or Hospitalization for Worsening Heart Failure

Primary Endpoint



No. at Risk		0	30	60	90	120	150	180	210
Placebo		317	234	159	87	41	16	6	1
Dronedarone		310	232	151	87	49	19	4	1

Number of Patients who Died: Placebo = 12; Dronedarone = 25

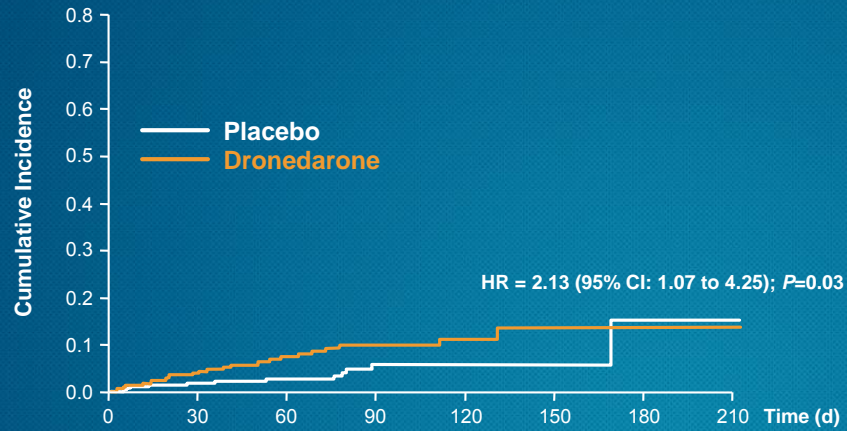
CI = confidence interval.
MULTAQ [package insert], sanofi-aventis US LLC, 2009.

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DR. KOWEY:

This study was terminated prematurely. For the reasons that dronedarone not only had a detrimental effect with regard to the prespecified primary endpoint, the prespecified primary endpoint was all cause mortality or hospitalization for heart failure.

ANDROMEDA: Cumulative Incidence of All-Cause Mortality



Patients at Risk		0	30	60	90	120	150	180	210
Placebo	317	256	181	103	50	18	6	1	
Dronedaron	310	257	174	104	59	22	5	1	

Number of Patients who Died: Placebo = 12; Dronedaron = 25

Køber L, et al. *N Engl J Med.* 2008;358:2678-2687.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

But the larger concern with this study was that there was an increase in all-cause mortality. There were excess number of deaths in patients that were treated with dronedaron at the time that this study was stopped, roughly a two to one ratio, compared to placebo.

Now, there have been all kinds of attempts to try to understand why this happened. I don't think that anybody really completely understands the reason for the adverse outcome in ANDROMEDA.

ANDROMEDA: Summary

- Conducted in patients with severe heart failure, recently hospitalized for decompensation, most of whom did not have AF¹
- Terminated early by DSMB due to 2-fold increase in mortality in dronedarone group²
- Patients may have been clinically improved at enrollment, and it is the history of decompensation that characterized them¹
 - Patients were predominantly NYHA class II and III
 - 38% had a history of AF/AFL (25% had AF at randomization)
- Main reason for death was worsening heart failure¹

1. MULTAQ [package insert]. sanofi-aventis US LLC: 2009.
2. Køber L, et al. *N Engl J Med*. 2008;358:2678-2687.

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DR. KOWEY:

But since it's there, it helps us to understand which patients with atrial fibrillation should not receive this drug. And we'll get into that a little bit later, but clearly, it's going to be a group of patients with severe heart failure. So an early terminated study, and the main reason for death was worsening heart failure.

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

ATHENA: Study Design and Overview

Objective¹

- Multinational, randomized, placebo-controlled study in patients with recent history of AF/AFL in SR or to be converted to SR

One of largest trials conducted in AF^{1,2}

- > 4600 patients at 551 sites in 37 countries^{1,2}
- > 1200 patients in US³

Patients representative of paroxysmal or persistent AF/AFL population¹

- ≥75 y with or without additional CV risk factors
- OR
- ≥70 y with ≥1 CV risk factor (HTN, DM, prior stroke/TIA, LAD ≥50 mm, LVEF <0.40)

Primary Endpoint

- Reduction in CV hospitalizations or death from any cause

Standard therapy permitted including beta-blockers, CCBs, digoxin, ACE inhibitors/ARBs, statins, oral anticoagulants, and aspirin*

*MULTAQ may interact with several agents listed above. Please see Important Safety Information included in this presentation.

HTN = hypertension; DM = diabetes mellitus; TIA = transient ischemic attack; LAD = left atrial diameter; CCBs = calcium channel blockers (limited to diltiazem, verapamil, and bepridil).
1. Hohnloser SH et al. *J Cardiovasc Electrophysiol*. 2008;19:69-73.
2. Hohnloser SH et al. *N Engl J Med*. 2009;360:668-678.
3. Data on file, sanofi-aventis.

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DR. KOWEY:

The last of these four trials is ATHENA, and the term "landmark" trial is bandied about. I know people use this term for lots of trials that may not necessarily be that important. This one I think deserves the term "landmark" because it was a large trial, it was an international trial, it was carried out in patients, as we already said, with vascular risk. But the biggest reason why this was an important trial was because of its primary endpoint. This trial sought to determine whether this antiarrhythmic drug could be responsible for a reduction in something that we care about, which is cardiovascular hospitalizations, or death from any cause.

So we have moved the paradigm substantially from reduction in symptoms, now, to what I think most of us would agree is a very meaningful clinical endpoint.

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.

ATHENA: Patient Selection

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • High-risk patients with a history of paroxysmal or persistent AF/AFL • Aged ≥ 75 y with or without additional risk factors • Aged ≥ 70 y and ≥ 1 risk factor (hypertension, diabetes, prior stroke/TIA, left atrium ≥ 50 mm, LVEF < 0.40) 	<ul style="list-style-type: none"> • Permanent AF • Unstable hemodynamic situation (ie, recently decompensated CHF) • NYHA class IV CHF • Bradycardia < 50 bpm and/or PR > 0.28 sec • 2nd or 3rd degree AV block or sick sinus syndrome (except when used in conjunction with a functional pacemaker) • QT Prolongation ≥ 500ms • Severe hepatic impairment • Calculated GFR at baseline < 10 mL/min • Potassium < 3.5 mmol/L • Concomitant use of strong CYP3A inhibitors • Concomitant use of drugs that prolong the QT interval and may induce torsade de pointes (ie, AAD use) • Severe illness limiting life expectancy • Pregnancy or breastfeeding

GFR = glomerular filtration rate.
Hohnloser SH, et al. *J Cardiovasc Electrophysiol* 2008;19:69-73.

Please see accompanying full prescribing information, including **boxed WARNING**.

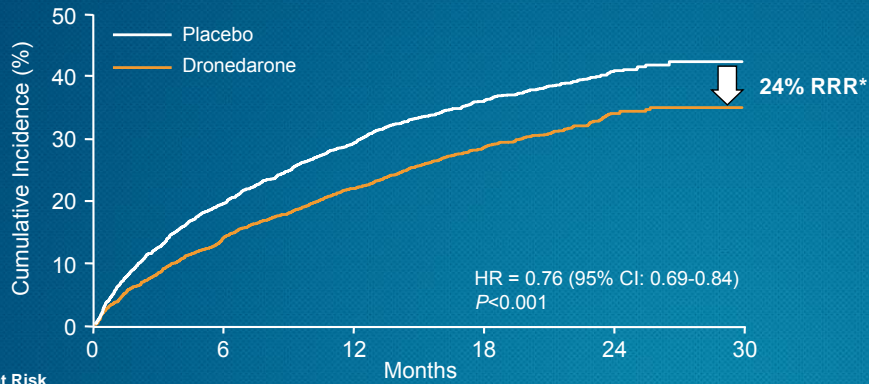
DR. KOWEY:

The patients who were enrolled in ATHENA, as we've already said, were elderly patients at vascular risk. The patients that were excluded from ATHENA important to understand were the usual patients that we don't treat with antiarrhythmic drugs, severe conduction disease, severe heart failure, patients who had severe organ impairment, et cetera. Those patients were excluded, and that's important because those exclusionary criteria form the basis for a lot of what you'll see in the package insert later.

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.

ATHENA: Significantly Reduced CV Hospitalizations

Primary Endpoint (Entirely attributable to the effect on CV hospitalizations)



Patients at Risk		0	6	12	18	24	30
Placebo		2327	1858	1625	1072	385	3
Dronedaron		2301	1963	1776	1177	403	2

Mean follow-up 21±5 months.
RRR = relative risk reduction.
MULTAQ [package insert], sanofi-aventis US LLC: 2009.

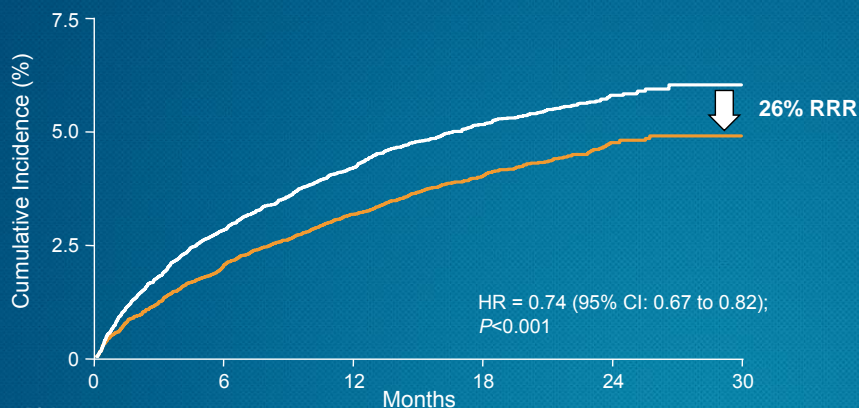
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DR. KOWEY:

This is the primary prespecified endpoint, the Kaplan-Meier curve for CV hospitalizations. And as you can see, this primary endpoint, it's CV hospitalizations and mortality combined, was significantly reduced, in this trial, the *P* value was very robust, with a hazard ratio of .76.

ATHENA: Significantly Reduced First CV Hospitalization

Secondary Endpoint



Patients at Risk	0	6	12	18	24	30
Placebo	2327	1858	1625	1072	385	3
Dronedaronone	2301	1963	1776	1177	403	2

Mean follow-up 21 ± 5 months.
DR = dronedaronone.
Hohnloser SH, et al. *N Engl J Med* 2009;360:668-678.

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DR. KOWEY:

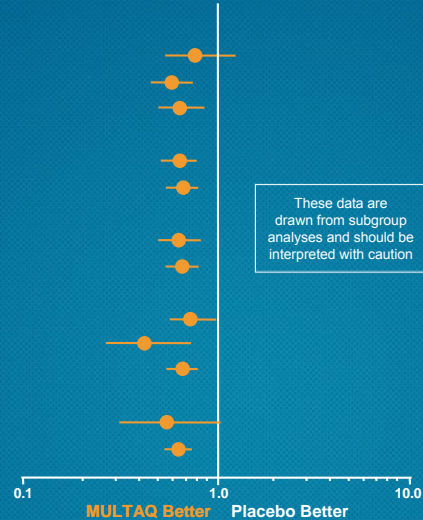
When one further dissects the data from ATHENA, you can see from this slide, that what drove the primary endpoint was a reduction in CV hospitalization. And what drove the CV hospitalization endpoint was a reduction in hospitalizations for atrial fibrillation. The reductions in things like ACS, as well, and heart failure, but what really drove this was what we would have expected from an atrial antiarrhythmic drug, that we had fewer patients going into the hospital for atrial fibrillation.

And these were real hospitalizations. These weren't overnight stays in the emergency department, these weren't incidental cardioversions, these were patient really hospitalized.

ATHENA: Consistent Results Across Patient Subgroups

Risk Reduction for Primary Endpoint Was Entirely Attributable to the Effect on CV Hospitalization

Characteristic	n	RR	P Value
Age (y)			
<65	873	0.89	
(65-75)	1830	0.71	
≥75	1925	0.75	0.27
Gender			
Male	2459	0.74	
Female	2169	0.77	0.65
AF/AFL			
Yes	1155	0.74	
No	3473	0.76	0.85
NYHA			
Class I or II	1165	0.80	
Class III	200	0.56	
No CHF	3263	0.76	0.22
LVEF (%)			
<35	179	0.68	
≥35	4365	0.76	0.58



*CCBs with heart rate-lowering effects restricted to diltiazem, verapamil, and bepridil.

RR = relative risk.

MULTAQ [package insert]. sanofi-aventis US LLC: 2009.

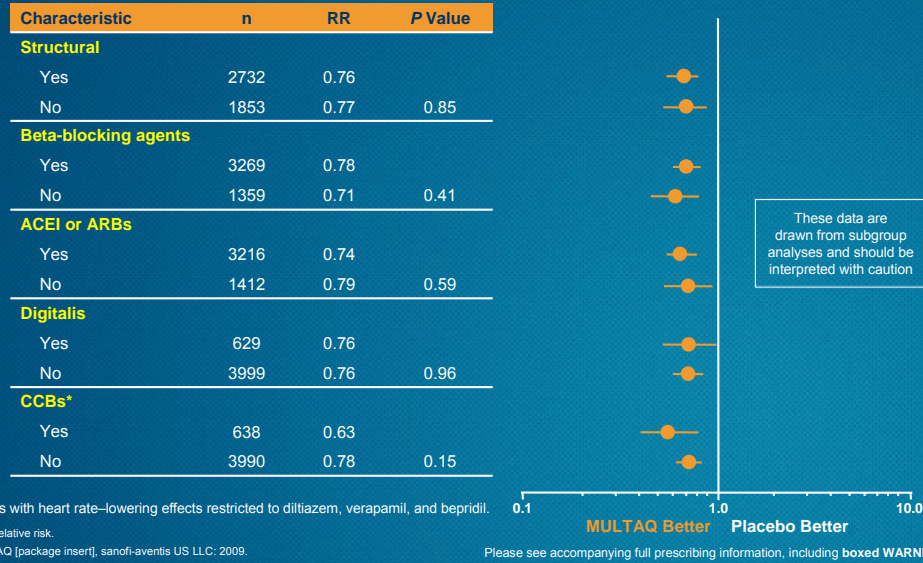
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DR. KOWEY:

The other piece of reassuring information, given that the size of the treatment effect, and the size of the trial, it is very logical to be able to go back, and in a very valid way, look at subgroups. And so this is the forest plot for many of the subgroups. The bottom line here, from this slide,

ATHENA: Consistent Results Across Patient Subgroups (cont'd)

Risk Reduction for Primary Endpoint Was Entirely Attributable to the Effect on CV Hospitalization



DR. KOWEY:

and from this slide, which is the continuation, is that it didn't matter if you were a man or a woman, young or old, low ejection fraction or normal ejection fraction, no matter what concomitant therapy that the patient's received, dronedarone fared better than placebo across all of those subgroups, a very robust treatment effect.

ATHENA: Summary

- MULTAQ is the first AAD to significantly reduce CV hospitalizations in paroxysmal or persistent AF with CV risk factors
- 24% reduction in the composite primary endpoint of CV hospitalization or death from any cause was entirely attributable to the effect of MULTAQ on CV hospitalizations
- 26% reduction in CV hospitalizations driven by fewer admissions for AF

MULTAQ [package insert]. sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

So what ATHENA taught us is that it is possible, as you brought forward earlier, Eric, it is possible, using an antiarrhythmic drug, to have a meaningful effect on endpoints that we really care about. Why do we want our patients to take antiarrhythmic drugs? Yeah, clearly, we want them to feel better. We'd also like to be able to keep them out of the hospital.

Differentiating the ATHENA and ANDROMEDA Patient

Types of CHF Patients	ATHENA	ANDROMEDA
Class I CHF	If clinically stable during the past month	Excluded
Class II CHF	If clinically stable during the past month	If hospitalized for heart failure or class IV symptoms within the last month
Class III CHF		
Class IV CHF	Excluded	If hospitalized for heart failure or class IV symptoms within the last month
	APPROPRIATE HF PATIENT	INAPPROPRIATE HF PATIENT

Data on file, sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

So now, what has come out of this I think is a very clear idea of who should not and who should receive this drug. Patients who should receive the drug are clearly those patients, like those patients in ATHENA who benefitted, patients who should not receive the drug are those patients described in the ANDROMEDA study, the patients with sick and advanced heart failure.

MULTAQ: Adverse Reactions From Pooled Data of Key Clinical Trials

Adverse Drug Reactions That Occurred in at Least 1% of Patients and Were More Frequent Than With Placebo

	Placebo (n=2875)	Dronedarone 400 mg BID (n=3282)
Gastrointestinal disorders		
Diarrhea	6%	9%
Nausea	3%	5%
Abdominal pain	3%	4%
Vomiting	1%	2%
Dyspeptic signs and symptoms	1%	2%
General disorders and administration-site conditions		
Asthenic conditions	5%	7%
Cardiac disorders		
Bradycardia	1%	3%
Skin and subcutaneous tissue disorders		
Including rashes (generalized, macular, maculopapular, erythematous), pruritus, eczema, dermatitis, dermatitis allergic	3%	5%

Photosensitivity reaction and dysgeusia have also been reported in <1% of patients treated with MULTAQ.

MULTAQ [package insert]. sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including **boxed WARNING**.

DR. KOWEY:

This slide summarizes the common adverse reactions that occurred across five clinical trials, ATHENA, EURIDIS/ADONIS, ERATO, and DAFNE. The most frequent adverse reactions observed with dronedarone were gastrointestinal--diarrhea, nausea, abdominal pain, vomiting, dyspepsia, and asthenia. Premature discontinuation due to adverse reactions occurred in about twelve percent of patients receiving dronedarone, and about seven and a half percent of the placebo-treated group. The most common reasons for discontinuation with dronedarone compared to placebo were gastrointestinal disorders and QT prolongation.

Important Safety Information

Contraindications

WARNING: HEART FAILURE

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.

MULTAQ is also contraindicated in patients with:

- Second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker), bradycardia <50 bpm, QTc Bazett interval ≥ 500 msec or PR interval >280 msec, and severe hepatic impairment. MULTAQ should not be given to patients who are or may become pregnant (Category X) or nursing. MULTAQ may cause fetal harm when administered to a pregnant woman

MULTAQ should not be coadministered with:

- Strong CYP3A inhibitors such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, ritonavir
- Drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine antipsychotics, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics

MULTAQ [package insert]. sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including **boxed WARNING**.

VOICE OVER SCRIPT:

The label for MULTAQ has a boxed WARNING regarding HEART FAILURE. 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.

MULTAQ is also contraindicated in patients with second- or third-degree atrioventricular (AV) block or sick sinus syndrome, bradycardia <50 bpm, QT interval ≥ 500 msec or PR interval >280 msec, and severe hepatic impairment. MULTAQ should not be given to patients who are or may become pregnant or nursing.

MULTAQ should not be coadministered with strong CYP 3A inhibitors, or drugs or herbal products that prolong the QT interval.

Important Safety Information (cont'd)

New or Worsening Heart Failure

- 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. Advise patients to consult a physician if they develop signs and symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath

Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

- 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

QT Interval Prolongation

- MULTAQ induces a moderate (average of about 10 msec but much greater effects have been observed) QTc (Bazett) prolongation. If the QTc Bazett interval is ≥ 500 msec, MULTAQ should be stopped

Increase in Creatinine

- 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]. sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including **boxed WARNING**.

VOICE OVER SCRIPT:

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. Advise patients to consult a physician if they develop signs and symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath.

Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

MULTAQ induces a moderate QT prolongation. If the QT interval is ≥ 500 milliseconds, MULTAQ should be stopped.

Serum creatinine levels increase by about 0.1 milligrams per deciliter (mg/dL) following MULTAQ treatment initiation. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. The change in creatinine levels has been shown to affect glomerular filtration.

Important Safety Information (cont'd)

Drug-Drug Interactions

- Treatment with Class I or III antiarrhythmics or drugs that are strong inhibitors of CYP 3A must be stopped before starting MULTAQ (see Contraindications)
- 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
- Increased digoxin levels and gastrointestinal disorders have been observed when MULTAQ was coadministered with digoxin
 - Digoxin can also 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]. sanofi-aventis US LLC: 2009.

Please see accompanying full prescribing information, including **boxed WARNING**.

VOICE OVER SCRIPT:

Treatment with Class I or III antiarrhythmics or drugs that are strong inhibitors of CYP 3A must be stopped before starting MULTAQ.

Patients should be instructed to avoid grapefruit juice beverages while taking MULTAQ, and beta-blockers could potentiate the effects of MULTAQ on conduction.

Increased digoxin levels and gastrointestinal disorders have been observed when MULTAQ was coadministered with digoxin.

Digoxin can also 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 Partnership for Appropriate Care and Treatment

Sanofi-aventis is committed to appropriate care and treatment

- mPACT Partnership was developed to assist health care professionals with identification of appropriate patients and to ensure safe use of MULTAQ while minimizing risk
- The risk mitigation program consists of a communication plan for health care professionals, a medication guide for patients, and postmarketing surveillance

Please see accompanying full prescribing information, including boxed WARNING.

VOICE OVER SCRIPT:

The MULTAQ Partnership for Appropriate Care and Treatment, or MPACT, was developed to assist healthcare professionals with identification of appropriate patients and to ensure safe use of MULTAQ while minimizing risk.

The risk mitigation program includes a communication plan for healthcare professionals, a medication guide for patients, and post-marketing surveillance.

For more detailed information and materials on the MPACT MULTAQ Program, please visit www.MULTAQ.com.

Features of MULTAQ

- **Outpatient Initiation**
 - No hospitalization needed
- **Dosing Regimen**
 - No loading dose; 400 mg BID with food
 - No clinically significant INR increase with warfarin
- **PK/PD Profile**
 - Low lipophilicity
 - Short half-life (13-19 hours)
 - No iodine; no associated toxicities
- **Only AAD with positive CV hospitalization data**

MULTAQ [package insert]. Bridgewater, NJ; sanofi-aventis US LLC: 2009.
Hohnloser SH, et al. *N Engl J Med*. 2009;360:668-678.

Please see accompanying full prescribing information, including boxed WARNING.

DR. KOWEY:

So, in summary, this is a very interesting new chemical entity. I think all of us would agree that there is no free skate in atrial fibrillation management. This is not a panacea. It's not for every patient. It's not going to work in every patient. And some patients aren't going to be able to tolerate it. But, it is a very useful addition to the therapeutics we currently have available. One of the things that I didn't mention that's very important is that the entire data set for dronedarone, including the ANDROMEDA Study, was an outpatient experience. So this is a drug that can be, in fact, should be started as an outpatient. No rationale for bringing patients into hospital. There is no loading dose. There is no alternative dose. It's 400 milligrams twice a day, and the recommendation is to use it with food, because there is a food fast effect that increases the bioavailability. Because of its PK/PD profile, it appears to be a much better behaved molecule, easier to start, easier to stop. And I think the data that we presented with regard to outcomes should be fairly convincing with regard to the applicability in a group of patients with vascular disease. So I want to thank you for the opportunity to present this really very interesting data set. I'm sure we'll have a lot of questions about it as well, Eric.

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