

## **AMIODARONE**

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**DISCLOSURES: NONE**

## **AMIODARONE**

- Antiarrhythmic
- Anti ischemic ( $\beta$  blocker,  $\text{Ca}^{++}$  blocker)
- Vasodilator ( $\text{Ca}^{++}$  blocker)
- Antioxidant
- Inotropic

AMIODARONE

## **AMIODARONE: ELECTROPHYSIOLOGIC EFFECTS**

- Prolongs refractoriness
- Slows conduction
- Effects are more pronounced at faster HR (“use dependency”)
- Given IV, little effect on atrial\* or ventricular refractoriness. Does slow AVN conduction acutely
- Low proarrhythmia incidence (1-2%)

\* Not expected to convert AF to SR

**AMIODARONE: ELECTROPHYSIOLOGIC EFFECT**

## **AMIODARONE: PHARMACOKINETIC PROPERTIES**

<b>Bioavailability</b>	<b>Variable (22-86%)</b>
<b>Elimination</b>	<b>Hepatic and intestinal</b>
<b>Elimination half-life</b>	
<b>Acute</b>	<b>3-21 hrs</b>
<b>Chronic</b>	<b>52.6 days</b>
<b>Therapeutic range</b>	<b>1.0 - 2.5 <math>\mu</math>g / mL</b>
<b>Protein binding</b>	<b>96%</b>
<b>Myocardial concentration</b>	<b>10-50x plasma</b>
<b>Plasma levels do not correlate with clinical effects</b>	

AMIODARONE: PHARMACOKINETIC PROPERTIES

## **IV AMIODARONE**

### **Rapid distribution:**

Serum levels decline to 10% of peak within  
1/2 to 1 hr after infusion

No dose adjustment required for pts with  
hepatic or renal failure, or LV dysfunction

### **Administration:**

Through central line (to avoid phlebitis)

No concurrent heparin (to avoid precipitate)

### **Dosing:**

Initial infusion: 150 mg / 10 min, then

1 mg / min x 6 hr, then 0.5 mg / min x 18 hr

Maintenance: 360 mg / 24 hr with  
150 mg supplements prn

## **IV AMIODARONE**

## **ELECTROPHYSIOLOGIC EFFECTS OF IV AMIODARONE**

### **No significant effects on:**

Action potential duration

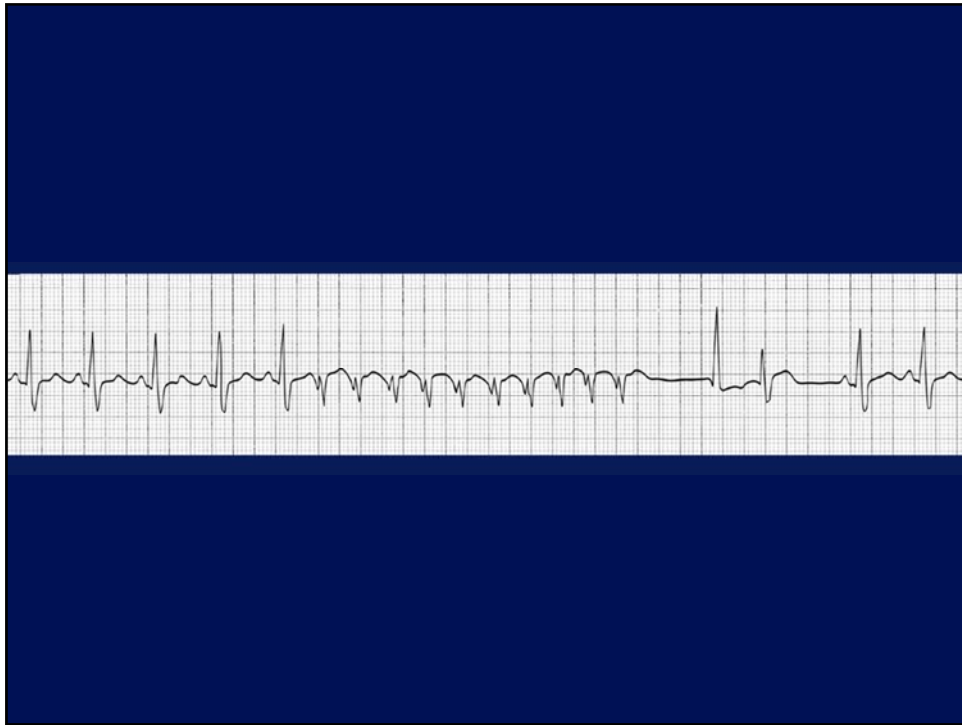
QT interval

Sinus rate

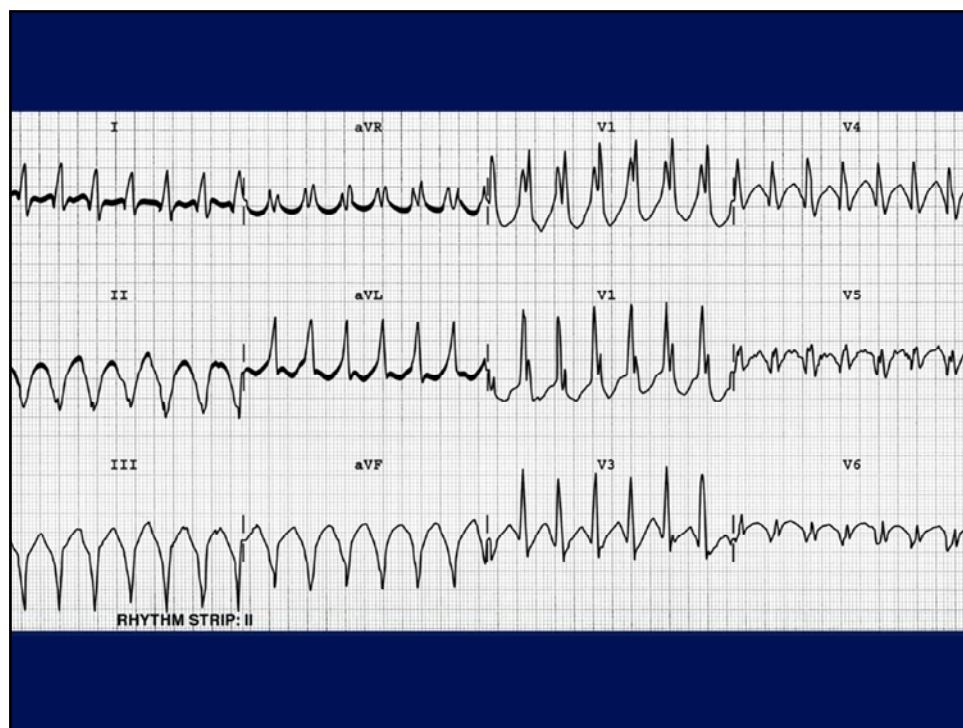
IV and infraHis refractory  
periods

**Prolongation of AV nodal  
conduction**

- ELECTROPHYSIOLOGIC EFFECTS OF IV AMIODARONE

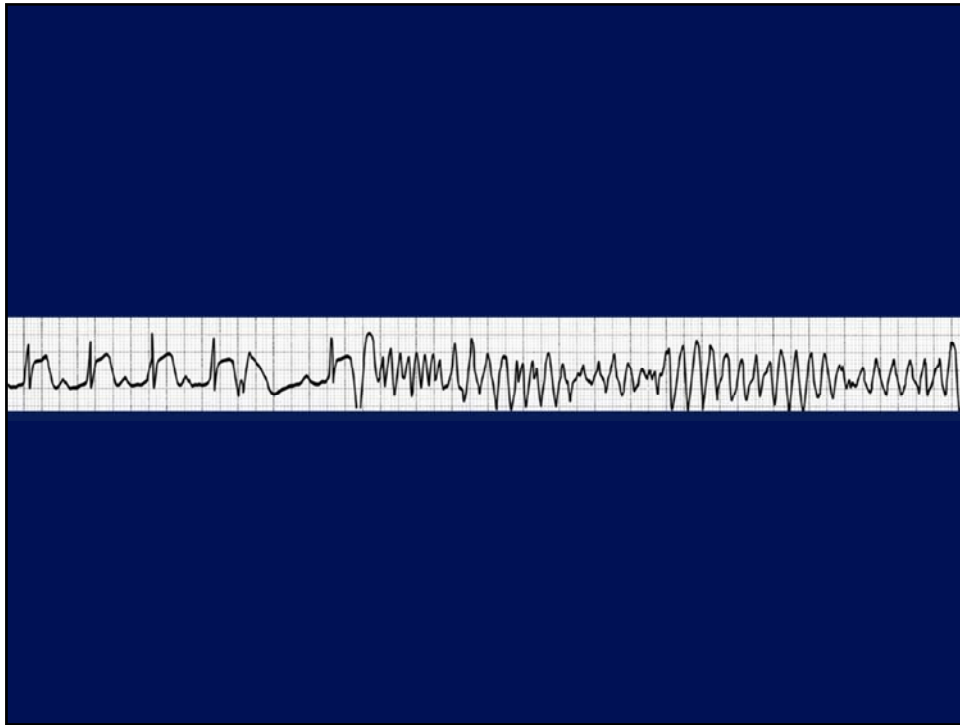


ecg



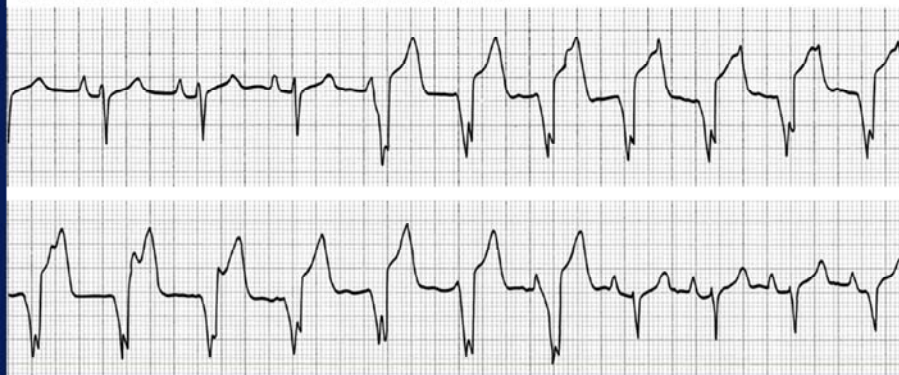
- VT Path 1



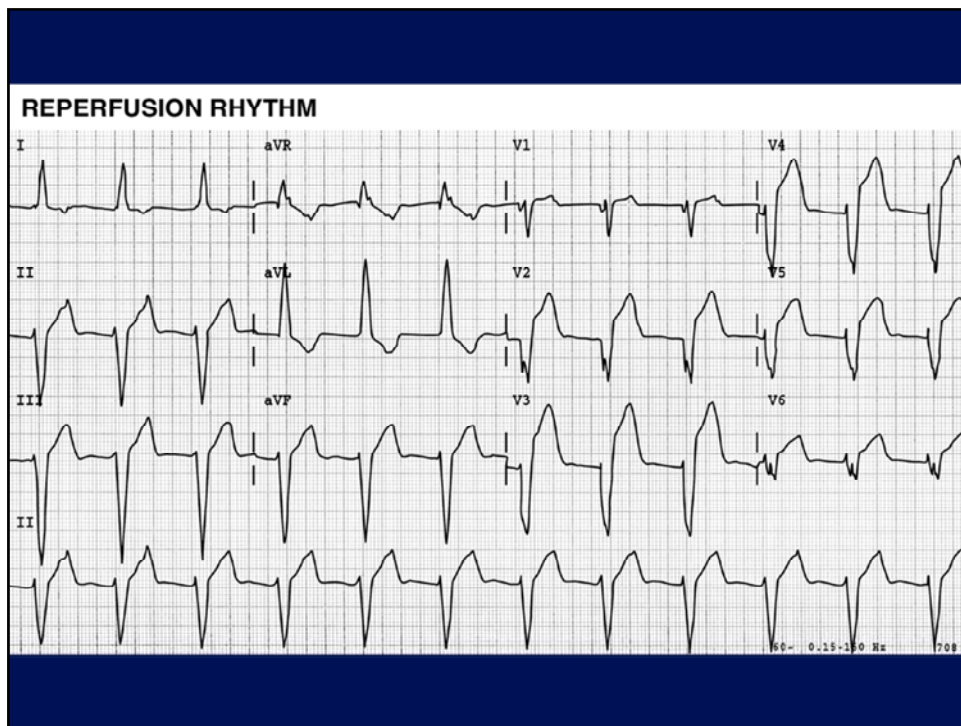


- Brady-dependant polymorphic VT

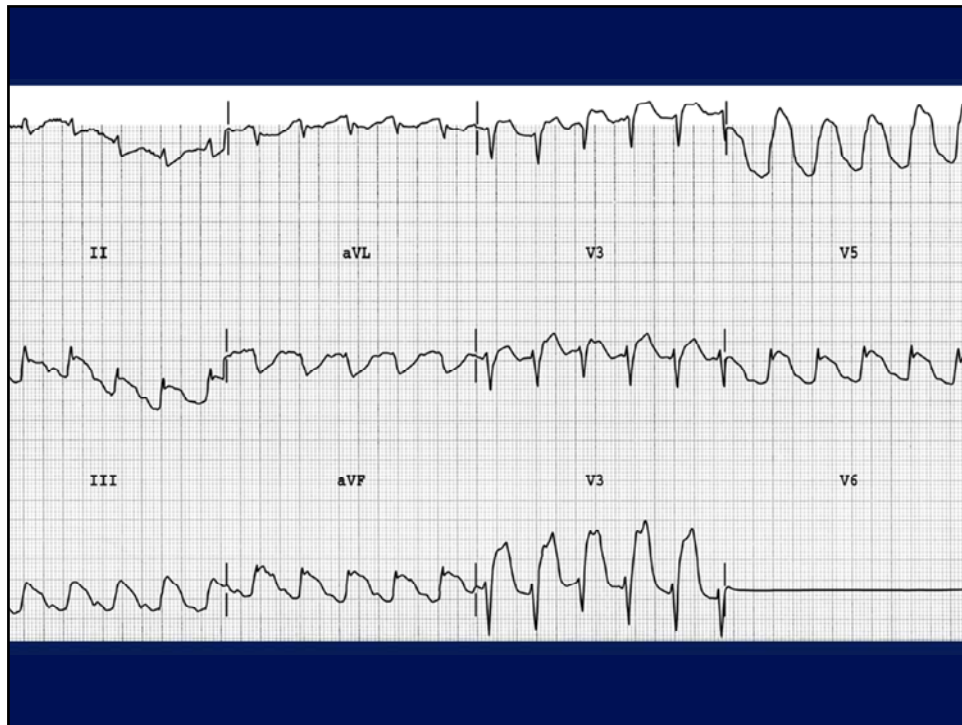
**ACCELERATED VENTRICULAR RHYTHM**



- Slow VT - Reperfusion



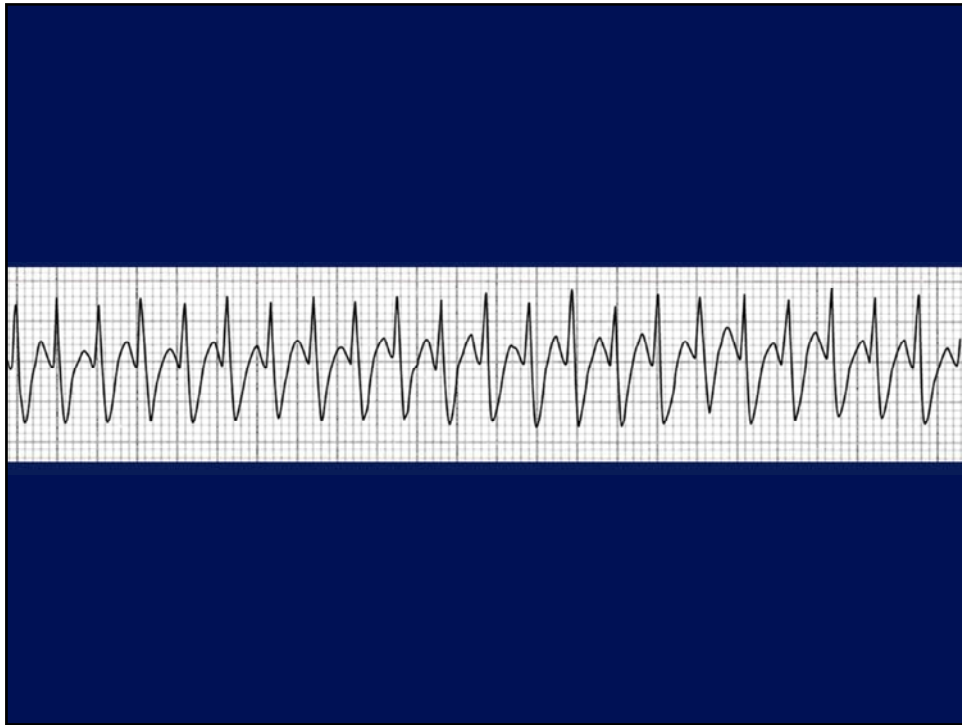
- Post PA AVR Ant. MI



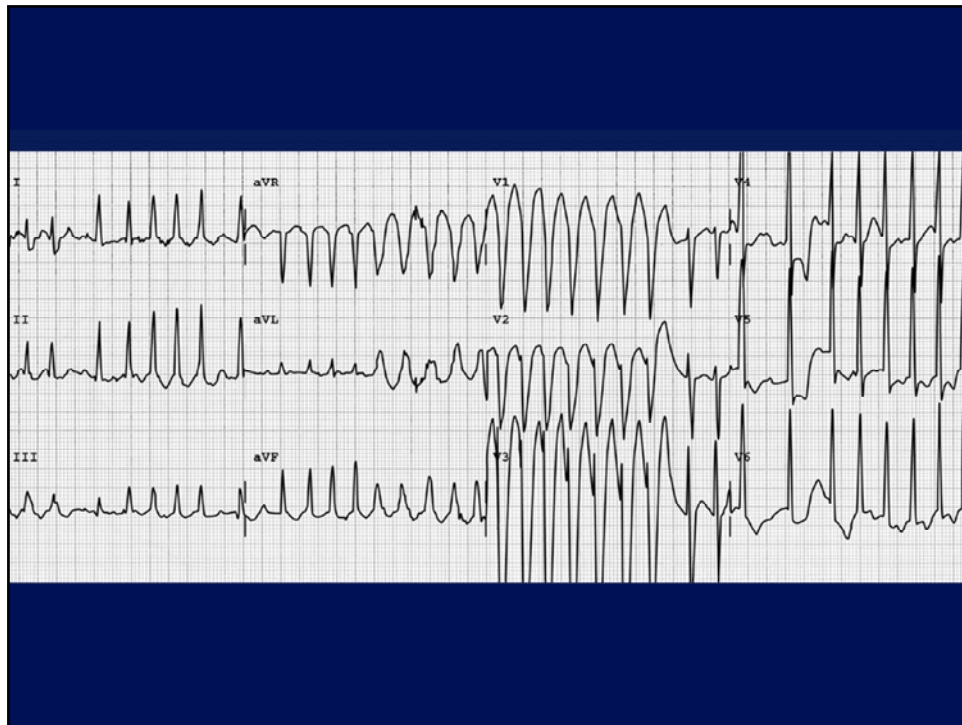
- ACUTE MI, NOT VT



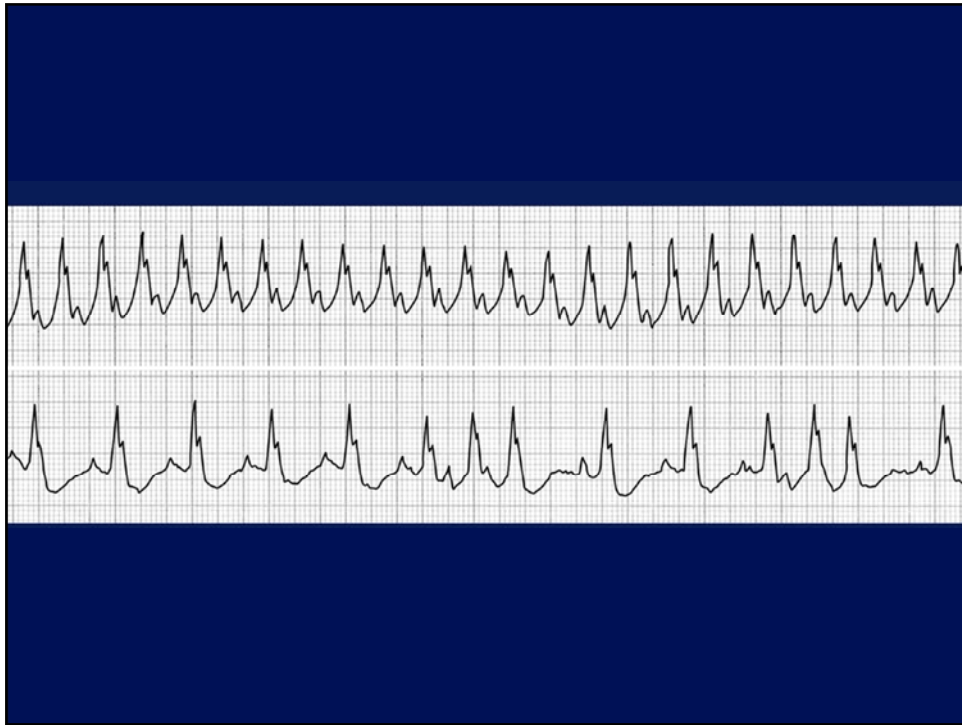
- CHEST PT, NOT VT



- FLUTTER 1:1



- AF, RATE=DEP, IV ABERRATION - NOT WPW



- AAT RESEMBLING VT



## **AMIODARONE: ORAL DOSING**

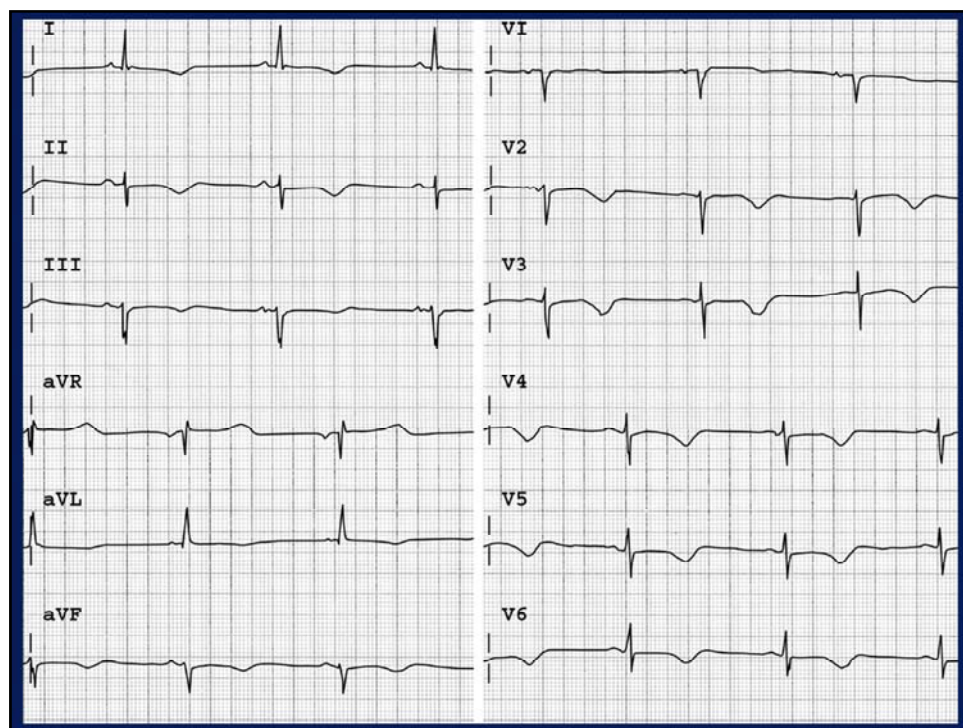
**Potentially lethal (ventricular arrhythmias):**

**800 - 1400 mg / day x 2-4 wks, then  
600 mg / day, then  
400 mg / day**

**Atrial fibrillation conversion:**

**600 - 1200 mg / day x 2 wks, then  
400 - 600 mg / day x 2 wks, then  
200 mg / day**

- AMIODARONE: ORAL DOSING



## **AMIODARONE IN AF**

- IV no better than placebo in restoring NSR acutely
- High single dose oral drug (30 / mg/kg)  
→ NSR in 50% at 8 hr, 80% at 24 hr if AF recent onset
- Most effective drug in preventing AF recurrence ( $\geq 60\%$ )
- Not FDA approved for use in AF

- AMIODARONE IN AF

## META-ANALYSIS OF AMIODARONE vs PLACEBO AND IC AARx IN AF OF ≤ 7 DAYS' DURATION

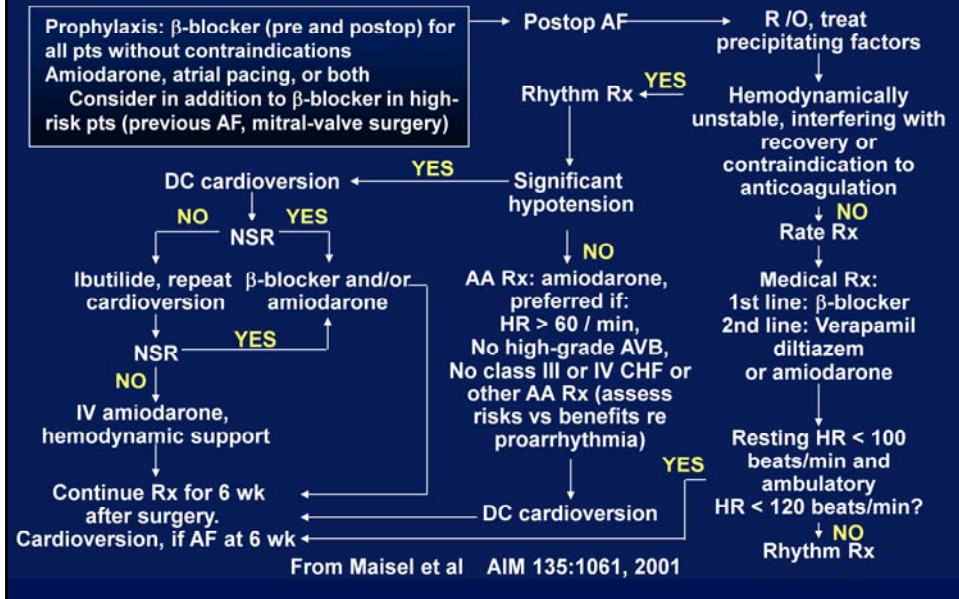
	<u>NSR</u>	<u>1 - 2 h</u>	<u>6 - 8 h</u>	<u>24 h</u>
Amio vs placebo	P = NS	< .02	< .001	
IC vs Amio	P < .001	< .001	NS	

Chevalier et al JACC 1.5.03  
 N = 595 RCT placebo  
 N = 579 RCT IC  
 Postop AF, excluded most drugs IV

**AF → NSR:  
SUMMARY OF META ANALYSIS FINDINGS**

- Amiodarone is ~ 44% more efficacious than placebo in restoring NSR
- Delay in amiodarone action 8 - 24 hr; inferior to IC agents up to 8 hr
- Added benefit of ↓ ventricular rate

## ALGORITHM FOR THE PREVENTION AND MANAGEMENT OF AF AFTER CARDIAC SURGERY



- ALGORITHM FOR THE PREVENTION AND MANAGEMENT OF AF AFTER CARDIAC SURGERY

## **AMIODARONE TO PREVENT AF DURING SURGERY**

**IV:** 4.5 G in 4-5 postop days,  
then 600 mg / day x 5 days

**Oral:** 4.5 G in 7 days, then 200 mg / day  
until discharge

Optimal regimen not defined

- AMIODARONE TO PREVENT AF DURING SURGERY

## ALGORITHM FOR Rx OF AF

**No  
structural  
heart  
disease**



**IA, IC or III  
(probably  
IC first)**

**Ischemic  
heart  
disease**



**IA or III  
(probably  
III first)**

**Mild-  
moderate  
LVH**



**IA, IC or III  
(probably  
IC first)**

**LV  
dysfunction**



**Amiodarone  
first**

- ALGORITHM FOR Rx OF AF



## **ATRIAL FIBRILLATION INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) SUBSTUDY OF AARx**

### **Inclusion criteria:**

- High risk pts (> 65 y.o., HT, DM, CHF, LAE > 5cm, prior TIA / CVA, EF < 40%)
- $\geq 6$  hr AF in past 6 mos
- 1 AF within prior 12 wks and not > 6 mos

**AARx:** Amiodarone, Sotalol, Class I agent

### **Endpoints:**

- NSR at 1 yr, on AARx, no cardioversions
- Time to 1st AF recurrence
- AF at 4 mos or 1 yr

NEJM 12/5/02 N = 4060 enrolled, 7401 screened

- ATRIAL FIBRILLATION INVESTIGATION OF RHYTHM  
MANAGEMENT (AFFIRM) SUBSTUDY OF AARx

## **ATRIAL FIBRILLATION INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) SUBSTUDY OF AARx**

### **Results:**

- Amiodarone superior to sotalol ( $P > .0004$ )
- Sotalol efficacy = Class I
- At 1 yr, IF cardioversion and  $\Delta$  drug, NSR in 80%
- At 1 yr, if NO cardioversion or  $\Delta$  drug, 30-50% in NSR
- 16% terminated amiodarone for any reason  
2 / 154 pulmonary fibrosis

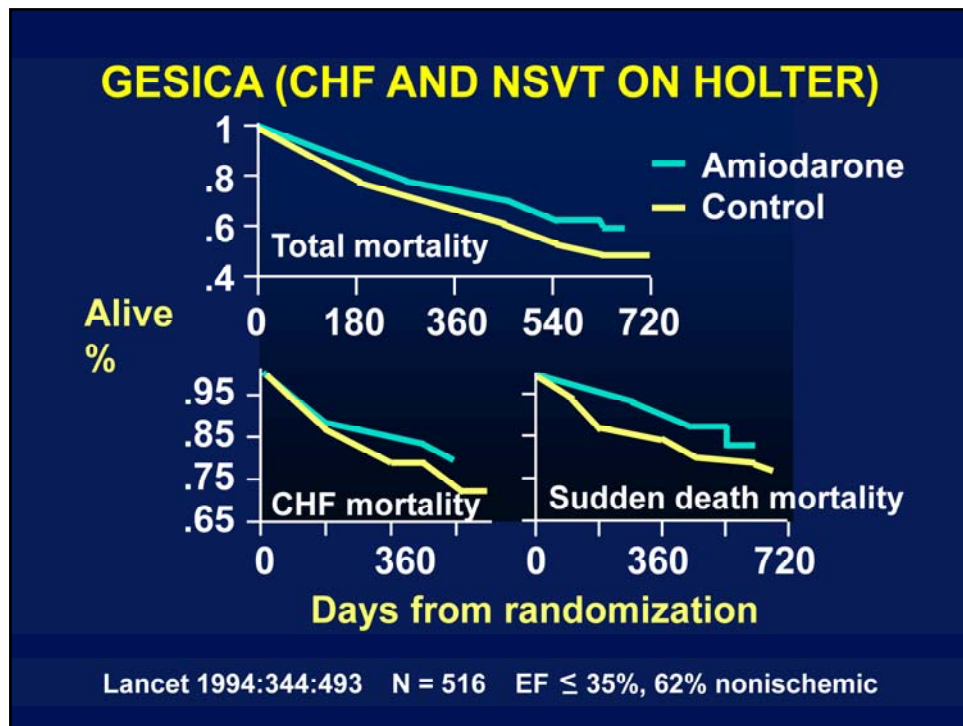
NEJM 12/5/02

# **ATRIAL FIBRILLATION INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM)SUBSTUDY OF AARx**

## **AMIODARONE vs PLACEBO IN PTS WITH SYSTOLIC DYSFUNCTION**

<b>GESICA</b>	Total mortality ↓ (non-ischemic cardiomyopathy)
<b>CHF-STAT</b>	No ↓ in mortality despite VEA ↓
<b>CAMIAT</b>	↓ arrhythmic death; no effect on total mortality (post-MI)
<b>EMIAT</b>	↓ arrhythmic death; no effect on total mortality (post-MI)

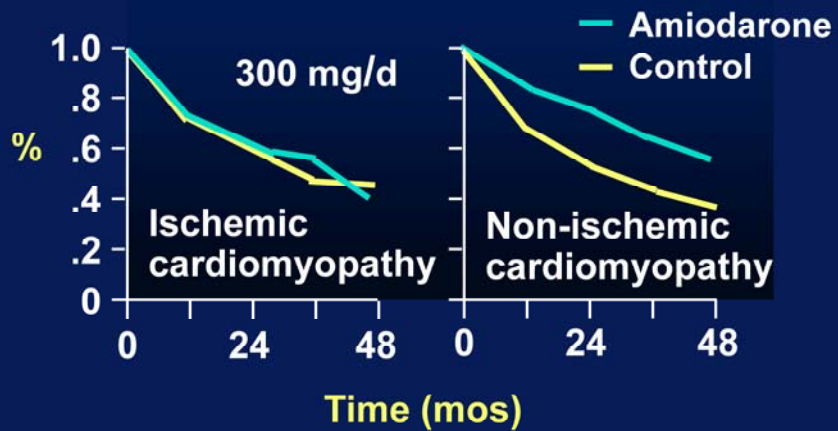
- AMIODARONE vs PLACEBO IN PTS WITH SYSTOLIC DYSFUNCTION



- GESICA (CHF AND NSVT ON HOLTER)

## CHF - STAT (CHF, $\geq 10$ PVCs/hr)

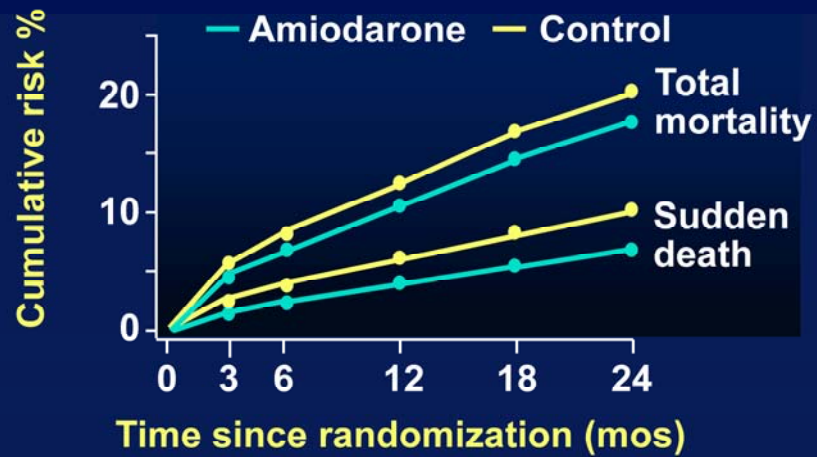
Survival without  
cardiac death or CHF hospitalization



Circulation 1996; 93:2128 N = 674, EF < 40%

- CHF - STAT (CHF,  $> 10$  PVCs/hr)

## META-ANALYSIS OF AMIODARONE EFFECT IN CHF AND POST MI PTS



Amiodarone Trials Meta-analysis Investigators.  
Lancet 1997; 350:1417 N = 6553

- META-ANALYSIS OF AMIODARONE EFFECT IN CHF AND POST MI PTS

## **AMIODARONE vs ICD IN PTS WITH VT: TRIALS DEMONSTRATING ICD SUPERIORITY**

<b>AVID</b>	Antiarrhythmics vs Implantable Defibrillators
<b>CIDS</b>	Canadian Implantable Defibrillator Study
<b>CASH</b>	Cardiac Arrest Study Hamburg
<b>MADIT-1</b>	Multicenter Automatic Defibrillator Implantation Trial (post MI pts)
<b>MUSTT</b>	Multicenter Unsustained Tachycardia Trial

- AMIODARONE vs ICD IN PTS WITH VT:TRIALS DEMONSTRATING  
ICD SUPERIORITYs

## **AMIOVIRT TRIAL**

**ICD vs Amiodarone in NIDCM: 1° prevention trial**

**Inclusions:** NIDCM

EF < 35%

NSVT (Asx)

NYHA I - III

**Randomization:** ICD vs amiodarone (n = 51,52)

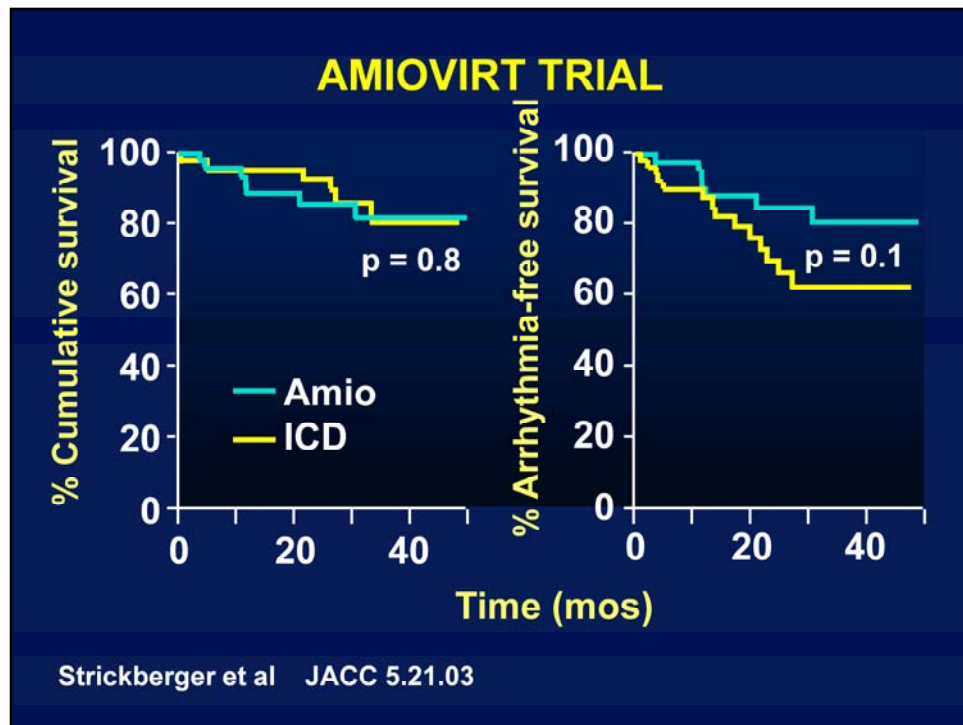
**Endpoints:** 1° - Total mortality

2° - Sudden death, non-sudden  
death, syncope, arrhythmia-  
free survival, QOL

**Study terminated early due to no effect**

Strickberger et al JACC 5.21.03





## SCD-HEFT TRIAL

- **N = 2521, NYHA II-III, EF  $\leq$  35%, ischemic (52%) + non-ischemic**
  - Conventional Rx + placebo –N =847
  - Conventional Rx + amio –N =845
  - Conventional Rx + shock-only ICD–N =829

Bardy et al NEJM 2005; 352:225

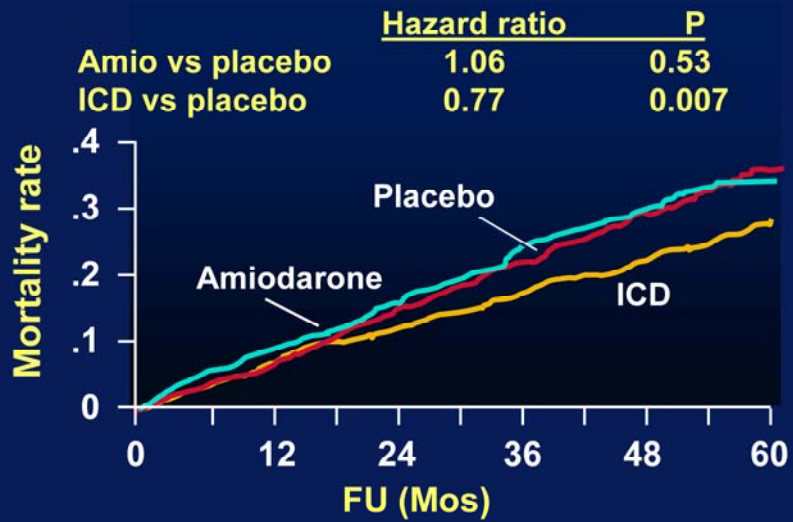
## SCD-HEFT TRIAL

- **1° endpoint - all-cause death**
  - Mean FU 46 mos; 32% D/C'd amio
  - 31% had shocks (7.5% / yr)
  - Of 244 deaths:
    - . Amio 28%; greater negative benefit in Class III pts
    - . Placebo 29%
    - . ICD 22%; greater benefit in Class III pts

**AMIODARONE HAS NO FAVORABLE EFFECT ON SURVIVAL AND MAY CONFER EXCESS RISK IN CLASS III PTS**

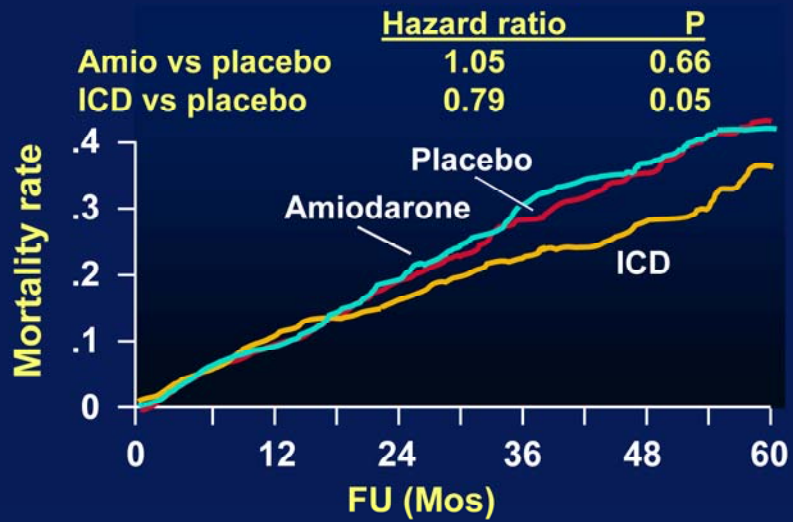
Bardy et al NEJM 2005; 352:225

## SCD-HEFT MORTALITY AND TREATMENT GROUP



Bardy et al NEJM 2005; 352:225

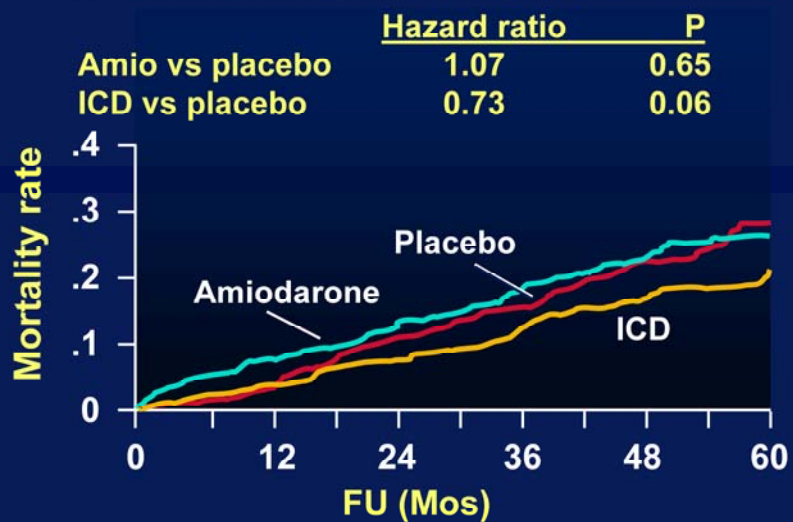
## SCD-HEFT DEATH BY CHF ETIOLOGY: ISCHEMIC



Bardy et al NEJM 2005; 352:225

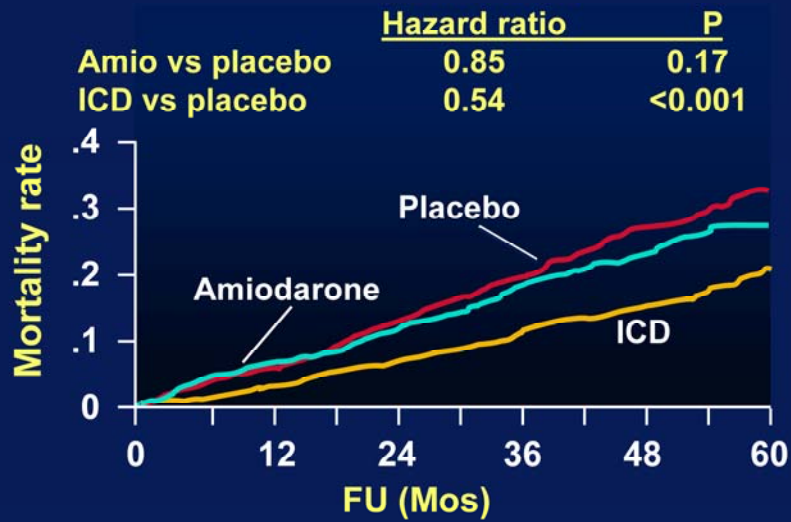
## SCD-HEFT

### DEATH BY CHF ETIOLOGY: NON-ISCHEMIC



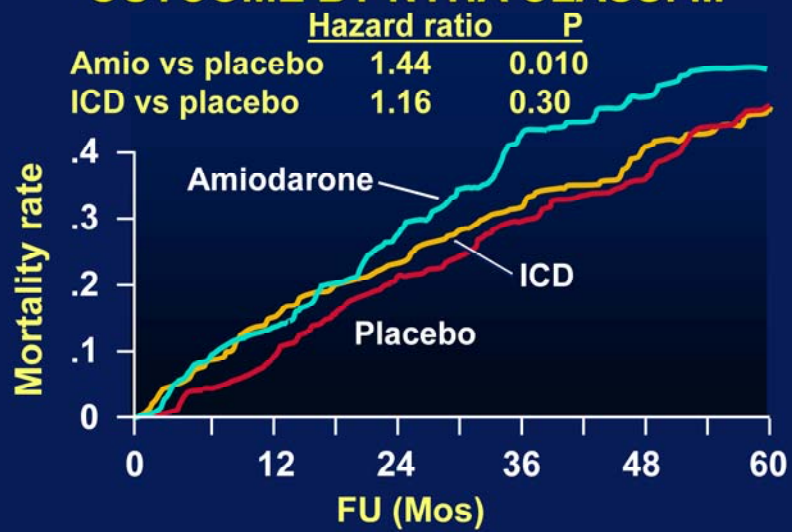
Bardy et al NEJM 2005; 352:225

## SCD-HEFT OUTCOME BY NYHA CLASS: II



Bardy et al NEJM 2005; 352:225

## SCD-HEFT OUTCOME BY NYHA CLASS: III



Bardy et al NEJM 2005; 352:225



# OPTIC\* Trial

412 patients receiving a St. Jude Medical dual chamber ICD, with 1) spontaneous VT; or 2) LVEF  $\leq$  40% with either spontaneous VF or inducible VT or VF.

Randomized

$\beta$ -Blocker Alone  
Metoprolol, Carvedilol,  
or Bisoprolol

Sotalol  
160 mg/day

$\beta$ -Blocker  
+ Amio  
800 mg load plus  
200 mg/day

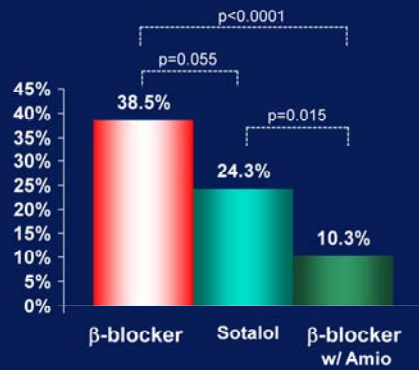
Endpoint (1 year):  
Occurrence of shock (appropriate or inappropriate)

\* Optimal Pharmacological Therapy in Implantable  
Cardioverter Defibrillator Patients Trial

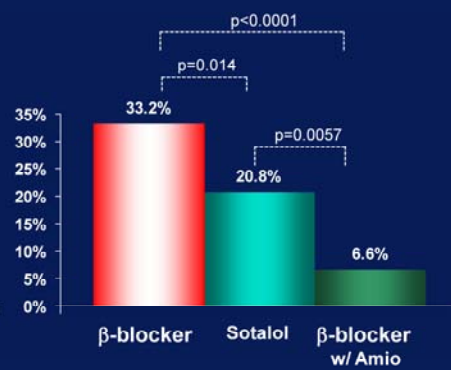
ACC Scientific Sessions 2005

# OPTIC Trial

## Any Shock at 1 Year



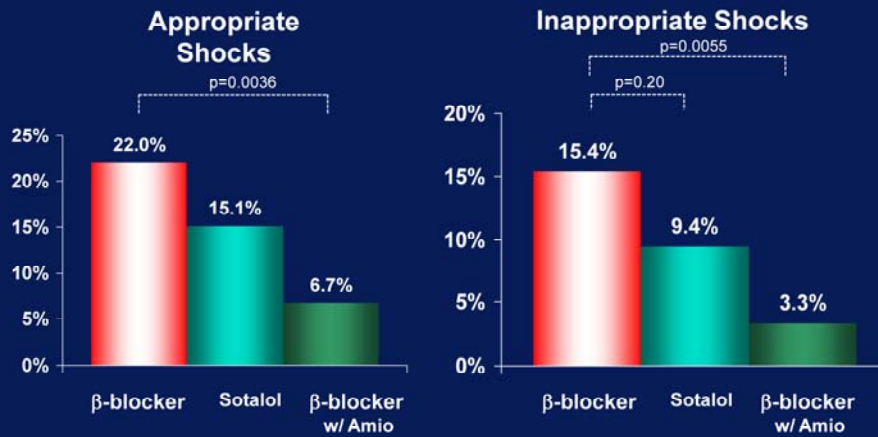
## Any Shock at 1 Year Excluding Shocks During First 21 Days



- Baseline clinical characteristics were similar between the treatment groups: 80% had prior MI, 29% inducible VT or VF and 71% spontaneous VT or VF.

ACC Scientific Sessions 2005

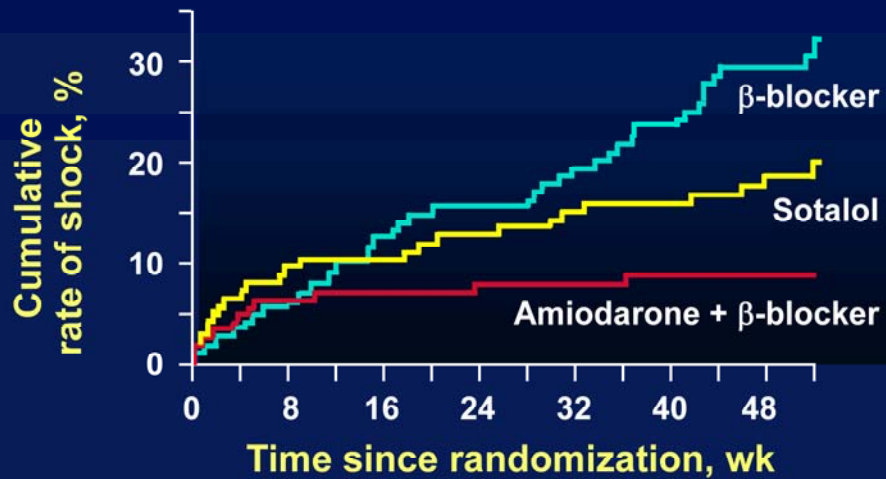
# OPTIC Trial



- Mean number of shocks per patient 4.32 in  $\beta$ -blocker alone group, 0.93 in sotalol group, and 0.51 of amio +  $\beta$ -blocker group.

ACC Scientific Sessions 2005

## OPTIC TRIAL: EFFECT OF DRUG Rx ON ICD SHOCKS



Connolly et al JAMA 2006; 295:165 N = 412

## OPTIC Trial: Summary

- Among patients receiving a dual chamber ICD for spontaneous or inducible VT or VF, sotalol and amiodarone +  $\beta$ -blocker were associated with  $\downarrow$  in shocks at 1 year compared with  $\beta$ -blocker alone.
- The reductions in the amiodarone plus  $\beta$ -blocker group were greater than the sotalol group.
- The addition of amiodarone or sotalol was associated with  $\downarrow$  in shock without an  $\uparrow$  in adverse events, suggesting these therapies may improve quality of life in patients with an ICD.

*ACC Scientific Sessions 2005*

## **AMIODARONE: MISCELLANEOUS EFFECTS**

- ↑ defibrillation threshold
- May ↑ pacing threshold
- Rare worsening of CHF (< 5%)
- Rare torsade de pointes
- Ibutilide can be used if ↑ QT is due to amiodarone
- Present in breast milk; crosses placenta
- Can cause fetal hypothyroidism, brain damage. Generally contraindicated in pregnancy

- AMIODARONE: MISCELLANEOUS EFFECTS

## **ADVERSE REACTIONS TO AMIODARONE**

	<b>Incidence (%)</b>	<b>Diagnosis</b>	<b>Management</b>
<b>Pulmonary</b>	<b>2</b>	<b>Cough and/or dyspnea, especially with local or high- resolution CT scan and decrease D<sub>L</sub>CO from baseline</b>	<b>Usually discontinue drug; steroids may be considered in more severe cases; rarely, continue with steroid if no other option</b>

Goldschlager et al, Heart Rhythm 2007

## **PULMONARY TOXICITY AND AMIODARONE**

- 5 - 15% of pts; rare at  $\leq 200$  mg / day
- Correlation with cumulative dose, but not serum drug level
- CXR: Interstitial pneumonitis, pneumonia, ARDS (rare), bronchiolitis obliterans (25% of cases)
- Characteristic presence of foamy macrophages in alveoli; cells contain amio-phospholipid complexes (due to drug absorption, not toxicity)
- Risk factors: preexisting pulmonary disease, dose  $> 400$  mg / day;  $\uparrow$  age; surgery; pulmonary angiography

- PULMONARY TOXICITY AND AMIODARONE



## **ADVERSE REACTIONS TO AMIODARONE**

	<b>Incidence (%)</b>	<b>Diagnosis</b>	<b>Management</b>
<b>GI</b>	<b>30</b>	<b>Nausea, anorexia and constipation</b>	<b>Symptoms may decrease with decrease in dose</b>
	<b>15-30</b>	<b>AST or ALT level &gt; 2 x normal</b>	<b>If hepatitis is considered, exclude other causes</b>
	<b>&lt;3</b>	<b>Hepatitis and cirrhosis</b>	<b>Consider discontinuation, biopsy, or both to determine whether cirrhosis is present</b>

Goldschlager et al, Heart Rhythm 2007

## ADVERSE REACTIONS TO AMIODARONE

	Incidence (%)	Diagnosis	Management
Thyroid	4-22 2-12	Hypothyroidism Hyperthyroidism	L-Thyroxine Steroids, propylthiouracil or methimazole; may need to discontinue drug; may need thyroidectomy.
Skin	<10 25—75	Blue Photosensitivity	Reassurance; decrease in dose Avoidance of prolonged sun exposure; sunblock; decrease in dose

Goldschlager et al, Heart Rhythm 2007

## **ADVERSE REACTIONS TO AMIODARONE**

<b>Incidence (%)</b>	<b>Diagnosis</b>	<b>Management</b>
<b>CNS 3-30</b>	<b>Ataxia, paresthesias peripheral polyneuropathy, sleep disturbance, impaired memory and tremor</b>	<b>Often dose dependent, may improve or resolve with dose adjustment</b>

Goldschlager et al, Heart Rhythm 2007

## **ADVERSE REACTIONS TO AMIODARONE**

	<b>Incidence (%)</b>	<b>Diagnosis</b>	<b>Management</b>
<b>Ocular</b>	<b>&lt;5</b>	<b>Halo vision, especially at night</b>	<b>Corneal deposits the norm; if optic neuropathy occurs, discontinue</b>
	<b>≤1</b>	<b>Optic neuropathy</b>	<b>Discontinue drug consult ophthalmologist</b>
	<b>&gt;90</b>	<b>Photophobia, blurring, and microdeposits</b>	

Goldschlager et al, Heart Rhythm 2007

## **ADVERSE REACTIONS TO AMIODARONE**

	<b>Incidence (%)</b>	<b>Diagnosis</b>	<b>Management</b>
<b>Heart</b>	<b>5</b>	<b>Bradycardia and AV block</b>	<b>May need permanent cardiac pacing</b>
	<b>&lt;1</b>	<b>Proarrhythmia</b>	<b>May need to discontinue drug</b>
<b>GU</b>	<b>&lt;1</b>	<b>Epididymitis and erectile dysfunction</b>	<b>Pain may resolve spontaneously</b>

Goldschlager et al, Heart Rhythm 2007

## **RECOMMENDED LABORATORY TESTING IN PATIENTS RECEIVING AMIODARONE**

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<b>Liver function tests</b>	<b>Baseline &amp; every 6 mo</b>
<b>Thyroid function tests</b>	<b>Baseline &amp; every 6 mo</b>
<b>Chest x-ray</b>	<b>Baseline &amp; yearly</b>
<b>Ophthalmologic evaluation</b>	<b>At baseline if visual impairment or for symptoms</b>

Goldschlager et al, Heart Rhythm 2007

## **RECOMMENDED LABORATORY TESTING IN PATIENTS RECEIVING AMIODARONE**

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**Pulmonary function  
tests (including  
D<sub>L</sub>CO)**

**Baseline and for  
unexplained cough or  
dyspnea, especially if  
underlying lung disease,  
suggestive x-ray  
abnormalities, & if  
clinical suspicion of  
pulmonary toxicity**

**Goldschlager et al, Heart Rhythm 2007**

## **RECOMMENDED LABORATORY TESTING IN PATIENTS RECEIVING AMIODARONE**

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<b>High-resolution CT Scan</b>	<b>If clinical suspicion of pulmonary toxicity</b>
<b>ECG</b>	<b>Baseline &amp; when clinically relevant</b>

Goldschlager et al, Heart Rhythm 2007



## **MAJOR DRUG INTERACTIONS WITH AMIODARONE**

<b>Drug</b>	<b>Interaction</b>
<b>Digoxin</b>	<b>Increased concentration and effect with sinus and AV node depression and GI tract and CNS toxicity</b>
<b>Warfarin</b>	<b>Increased concentration and effect</b>
<b>Quinidine, procainamide, disopyramide</b>	<b>Increased concentration and effect, torsade de pointes VT</b>
<b>Diltiazem, verapamil</b>	<b>Bradycardia and AV block</b>

Goldschlager et al, Heart Rhythm 2007

## **MAJOR DRUG INTERACTIONS WITH AMIODARONE**

<b>Drug</b>	<b>Interaction</b>
<b>β Blockers</b>	<b>Bradycardia and AV block</b>
<b>Flecainide</b>	<b>Increased concentration and effect</b>
<b>Phenytoin</b>	<b>Increased concentration and effect</b>
<b>Anesthetic drugs</b>	<b>Hypotension and bradycardia</b>
<b>Cyclosporine</b>	<b>Increased concentration and effect</b>
<b>Simvastatin, atorvastatin</b>	<b>Can promote liver function abnormalities</b>

Goldschlager et al, Heart Rhythm 2007

## **WHEN TO REFER TO AN ELECTROPHYSIOLOGIST**

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- **Worsening arrhythmia symptoms**
- **Evidence of amiodarone toxicity requiring changes in drug dosing or drug discontinuation. Until the arrhythmia problem stabilizes the patient may require intensified monitoring, EPS, ablative therapy, or pacemaker or ICD implantation.**
- **Repeat defibrillation threshold testing recommended for patients with ICD due to drug effect of increasing this threshold.**
- **Assess amiodarone-induced slowing of VT rate in patients with an ICD such that VT would not be detected by the device and therapy not delivered.**
- **Pregnant patients**
- **Pediatric patients**

Goldschlager et al, Heart Rhythm 2007

## **WHEN TO CONSULT A PULMONOLOGIST**

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- **Abnormal chest radiography at baseline or follow-up.**
- **Abnormal pulmonary function tests (particularly forced vital capacity and ( $D_LCO$ )) at baseline or follow-up.**
- **New cough and/or dyspnea, especially if otherwise unexplained or unexpected.**

Goldschlager et al, Heart Rhythm 2007

## **WHEN TO CONSULT AN ENDOCRINOLOGIST**

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- Any time hyperthyroidism is suspected (even if suppression of TSH is mild and subclinical disease is possible).
- An acutely ill patient where interpretation of TFTs will be complicated by euthyroid sick syndrome.
- When considering treating subclinical hypothyroidism.

Goldschlager et al, Heart Rhythm 2007