Managing the Safety of Drugs for Atrial Fibrillation

First Worldwide Internet Symposium on Drug-Induced QT Prolongation October 2007

International Society of Holter and Noninvasive Electrocardiology (ISHNE)

James P. Daubert, MD, Burr Hall , MD,
Thomas Sawyer, MD, Brett Faulknier, DO

University of Rochester Medical Center/ Strong Memorial Hospital
Cardiac Electrophysiology Section
Division of Cardiology / Department of Medicine
Rochester, New York, USA

Session Goals…

- Following This Session You Will Understand More Regarding:
  - Patient factors that relate to safety in prescribing drugs for atrial fibrillation
  - Individual drugs, safety profiles, common side effects, drug-drug interactions, and potential proarrhythmic effects as they relate to the treatment of atrial fibrillation
  - Treatment for common drug toxicities encountered during the therapy of atrial fibrillation
  - Measurement of QT interval and the calculation of "corrected" QT interval
  - Concept of transmural dispersion of repolarization
    - Review of recent literature
  - Genetic basis for Acquired LQTS
  - Emergent and long term management of torsade de pointes

Choose Wisely…

- Safety Issues Include
  - Drug induced proarrhythmia
  - Mortality
  - Bradyarrhythmias
  - Negative inotropic effect
  - Subjective and end organ toxicity
  - Safety of outpatient initiation
  - Drug metabolism
  - Avoidance of drug-drug interactions
  - Avoidance of drug-device interactions

Patient Factors

- Heart Failure
  - Prone to ventricular proarrhythmic effects
    - Myocardial vulnerability
    - Electrolyte imbalance
  - Indicated for low EF / CHF patients
    - Amiodarone
    - Dofetilide
    - Sotalol (avoid if decompensated/NYHA III-IV)
    - Azimilide?

Heart Failure / CHF-STAT

- CHF – STAT
  - 103 pts with CHF and AF at baseline. Randomized to Amiodarone vs. placebo
- Significantly higher rates of conversion and maintenance of NSR with Amiodarone

TABLE 2. Spontaneous Conversion to Sinus Rhythm and Onset of New AF With Amiodarone vs Placebo During 4-Year Follow-Up

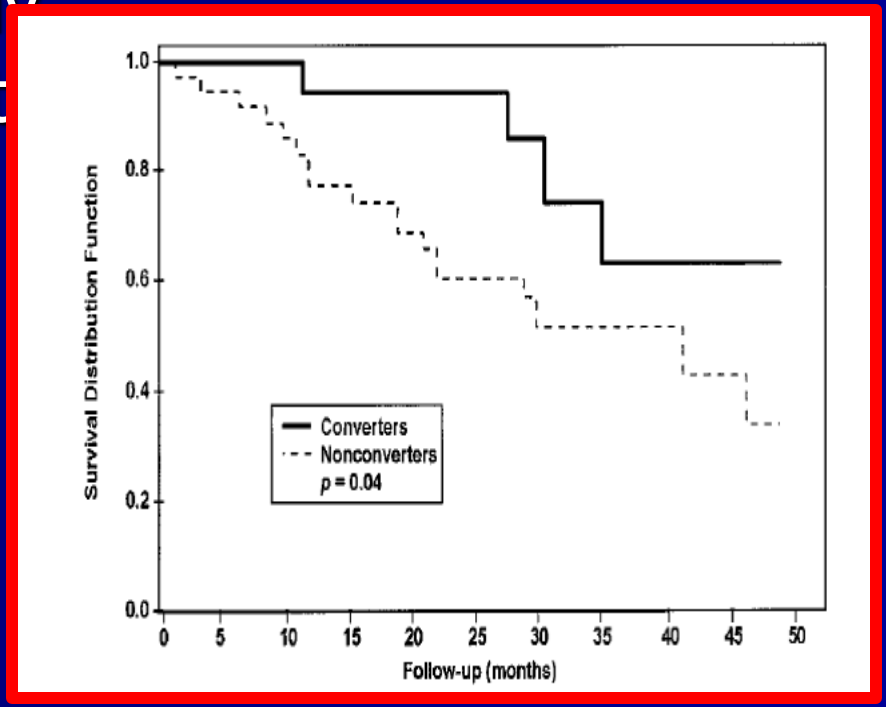
	Amiodarone (n=330)	Placebo (n=337)
Sinus rhythm	268	263
AF at randomization	51	52
AF Always	35	48
Converted to NSR	16	4*
AF New-onset	11	22†

NSR indicates normal sinus rhythm.
*χ^2=9.23 (P=0.002).
†χ^2=12.88 (P=0.005).

Massie. Circulation 1996;93(12):2128-34

Heart Failure / CHF-STAT

- Survival significantly improved in CHF pt who converted to NSR



Massie. Circulation 1996;93(12):2128-34

Heart Failure

- Danish Investigations of Arrhythmias and Mortality on Dofetilide in Heart Failure (DIAMOND-CHF)
- 1518 pts NYHA III/IV and EF ≤ 35%
  - Dofetilide vs. placebo
- Primary endpoint all-cause mortality

Torp-Pedersen. NEJM 1999;341(12):857-65

Heart Failure / DIAMOND-CHF

- No effect on all-cause mortality

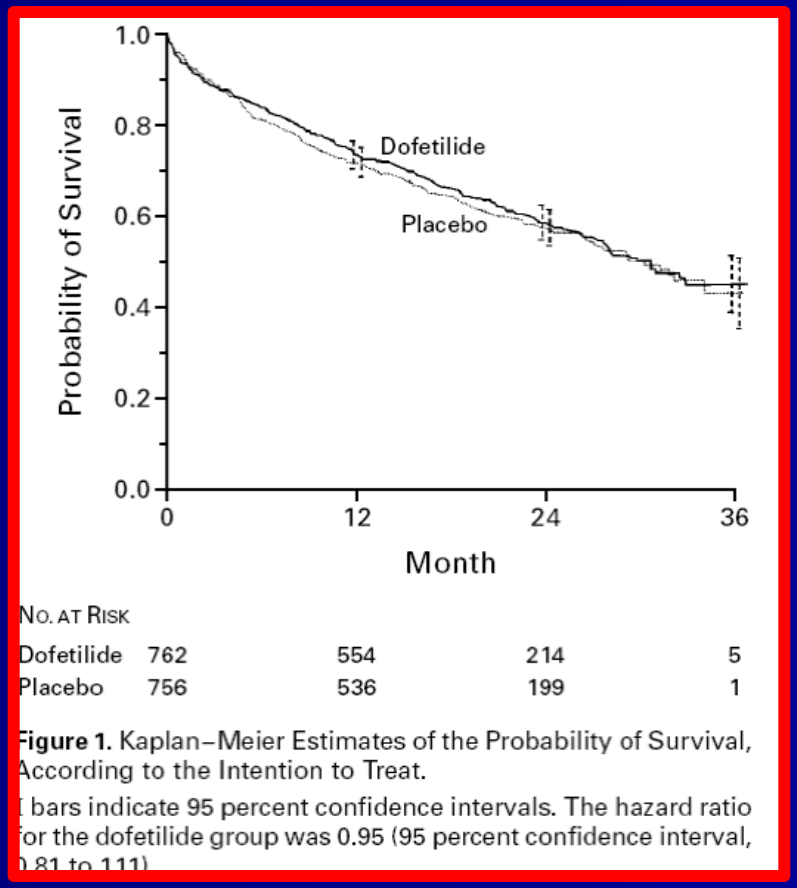


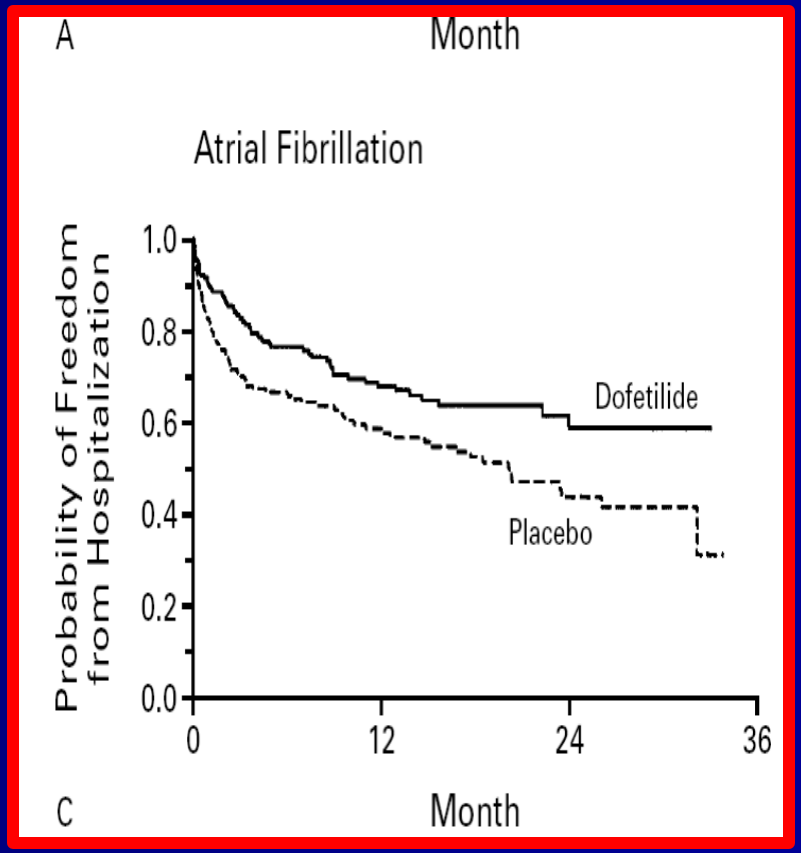
Figure 1. Kaplan–Meier Estimates of the Probability of Survival, According to the Intention to Treat.

bars indicate 95 percent confidence intervals. The hazard ratio for the dofetilide group was 0.95 (95 percent confidence interval, 0.81 to 1.11).

Torp-Pedersen. NEJM 1999;341(12):857-65

Heart Failure / DIAMOND-CHF

- Recurrent hospitalization significantly less in Dofetilide group



Torp-Pedersen. NEJM 1999;341(12):857-65

Heart Failure / DIAMOND-CHF

- 3.3% risk of torsade de pointes!
- Requires inpatient monitoring for drug initiation

TABLE 4. CLASSIFICATION OF VENTRICULAR ARRHYTHMIAS BY THE ARRHYTHMIA EVENTS COMMITTEE.

EVENT	DOFETILIDE (N=762)	PLACEBO (N=756)
	number (percent)	
Torsade de pointes	25 (3.3)	0
Before change in dosing protocol	7 (4.8)*	—
After change in dosing protocol	18 (2.9)†	—
Polymorphic ventricular tachycardia	3 (0.4)	4 (0.5)
Monomorphic ventricular tachycardia	12 (1.6)	13 (1.7)
Ventricular fibrillation	13 (1.7)	12 (1.6)

Torp-Pedersen. NEJM 1999;341(12):857-65

Heart Failure

- Mainstay therapies
  - Beta-blockers
  - ACE inhibitors and/or Angiotensin II receptor blockers
    - Control HR
    - Improve ventricular function
    - Prolong survival
    - ACE inhibitors reduce incidence of atrial fibrillation

Patient Factors

- Coronary artery disease
- Hypertensive heart disease
- Hypertrphic CM
- Hyperthyroidism
- Pulmonary disease
- WPW
- Special Populations
  - Pregnancy
  - Elderly
  - Renal dysfunction / CKD

Coronary Artery Disease

- Beta blockers indicated
- Antiarrhythmic therapy
  - Sotalol
  - Amiodarone
  - Dofetilide
  - Azimilide ?

Beta Blockers

- Safety / benefit of beta blockers in CAD well established
- Toprol XL superior to placebo in preventing AF recurrences after conversion
- May be as effective as low dose sotalol

Kuhlkamp. JACC2000;36:139
Steeds. Heart 1999;82:170

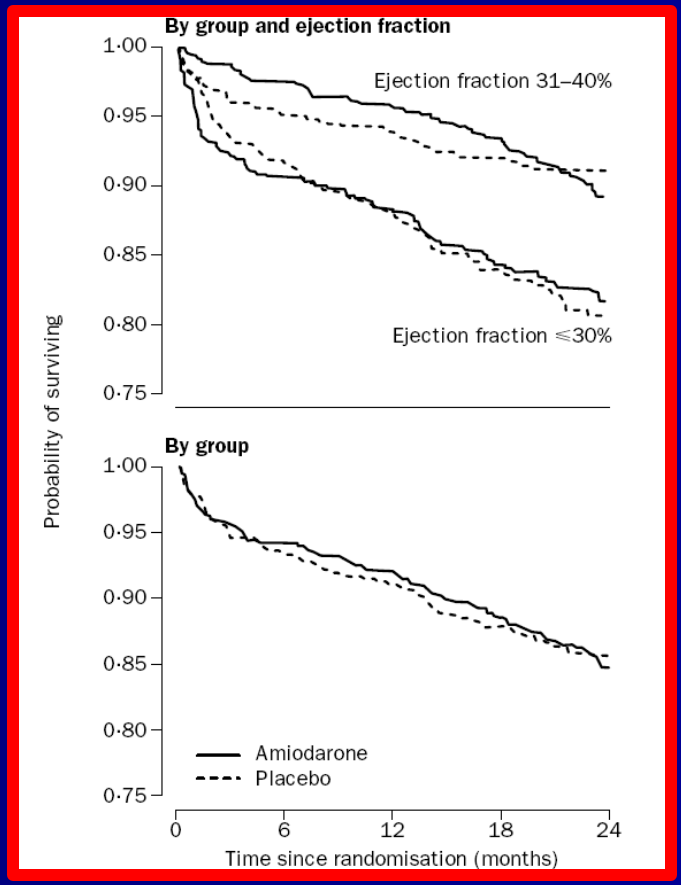
Sotalol: Post MI Study
n=1456 Randomized 60:40

- Deaths:
  - Sotalol 64 (7.3%)
  - Placebo (52 (8.9%)
  - p=NS
  - significant reduction in confirmed reinfarction (but not "suspected MI")

Julian, Lancet 1982;1:1142-47

Amiodarone

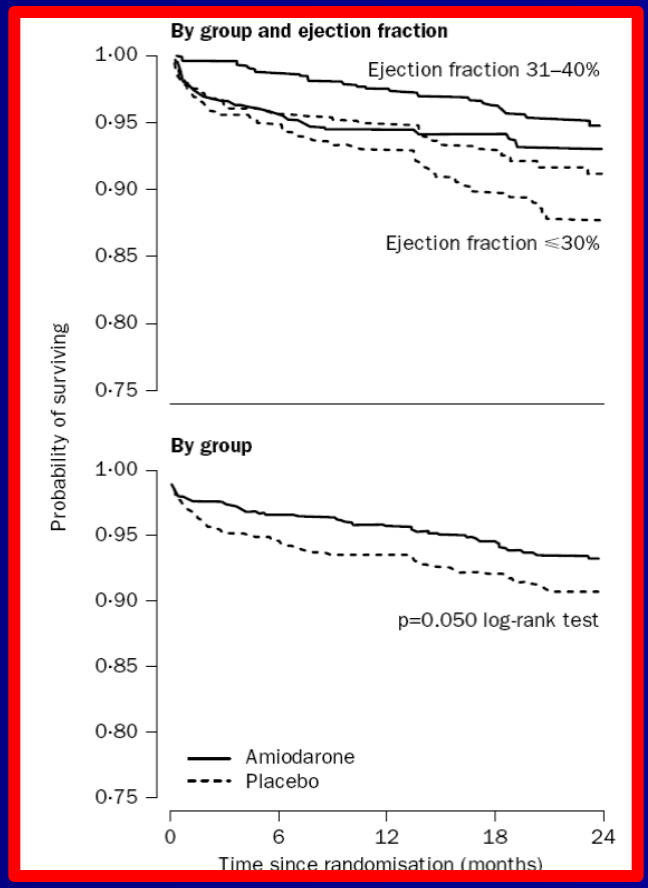
- EMIAT
- 1486 pts post-MI
- EF < 40%
- Amiodarone vs. placebo
- Primary endpoint
  - All-cause mortality
- Neutral mortality effect



Julian. Lancet 1997;349:667-74

Amiodarone

- EMIAT
- 35% risk reduction in arrhythmic deaths among amiodarone treated patients



Julian. Lancet 1997;349:667-74

Azimilide

- A-COMET
- Azimilide vs placebo vs Sotalol in pts with AF and planned cardioversion
- > 75% with structural heart disease
- Anti-arrhythmic efficacy of azimilide
  - slightly superior to placebo
  - significantly inferior to sotalol in patients with persistent AF
  - modest anti-arrhythmic efficacy and high rate of TdP and marked QTc prolongation limit azimilide utilization for the treatment of AF

 Lombardi. EHJ 2006 27(18):2224-2231

Azimilide - Saftey

Table 2 Number of patients with death, torsades de pointes, VT/VF, and MACE during the loading and whole study period

	Loading period			Whole study period		
	Azimilide ($n = 211$)	Sotalol ($n = 223$)	Placebo ($n = 224$)	Azimilide ($n = 211$) (%)	Sotalol ($n = 223$)	Placebo ($n = 224$)
Deaths	0	1	0	4 (1.9)	4	0
Torsade de pointes	1	0	0	5 (2.4)	0	0
Ventricular fibrillation	0	0	0	1 (0.5)	0	0
Patients with MACE (%)	1 (0.5)	1 (0.4)	0	9 (4.3)	4 (1.8)	0

VT/VF, ventricular tachycardia/ventricular fibrillation; MACE, major arrhythmic cardiac events. Note that individual patients may have more than one MACE.

2.4% rate of TdP in Azimilide group unexpectedly high; but absence of TdP in sotalol an underestimate

Lombardi. EHJ 2006 27(18):2224-2231

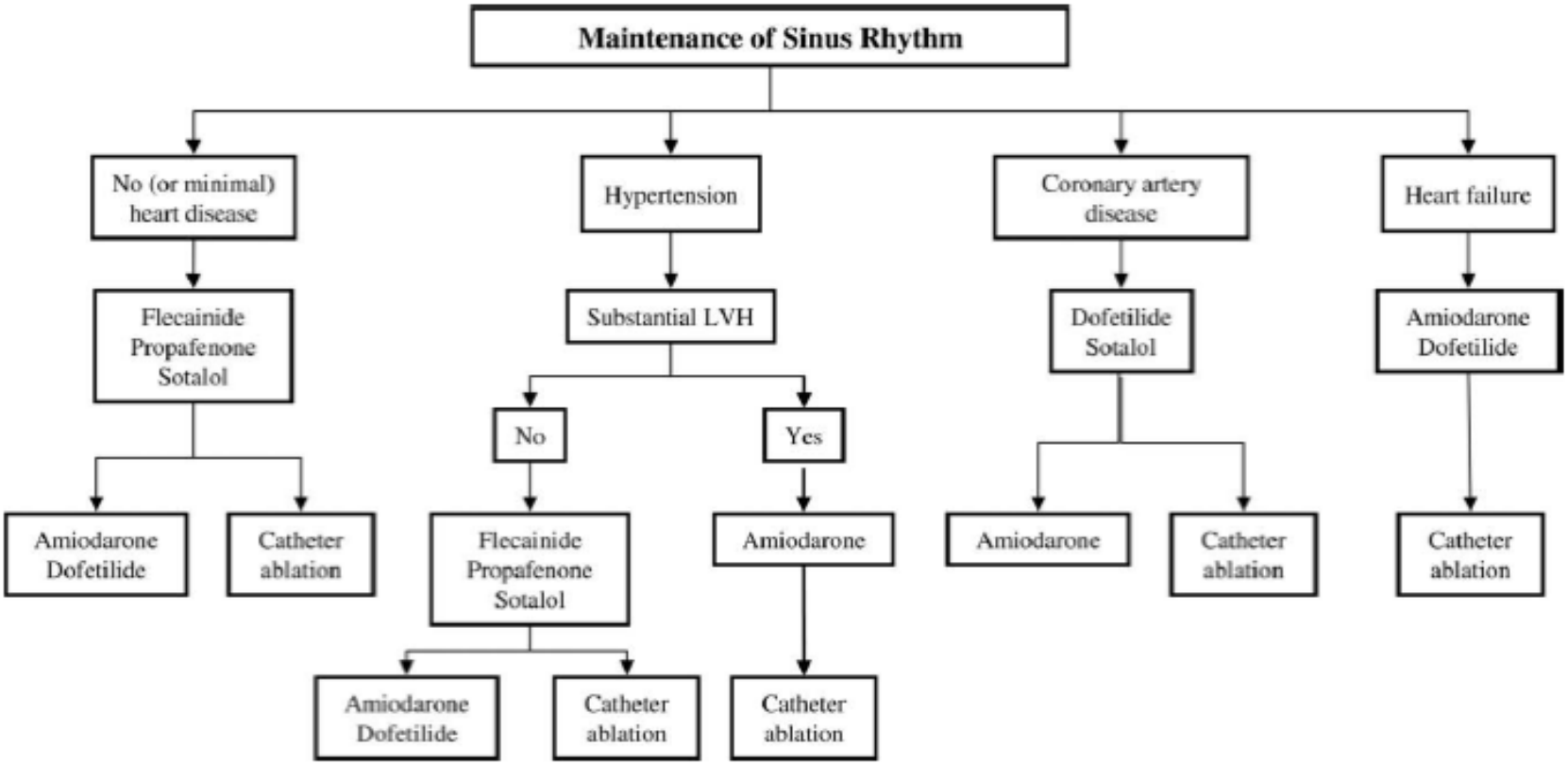
Patient Factors

- Hypertensive Heart Disease if "significant" LVH
  - Increased risk of Torsades de Pointes
    - ? Related to hypertrophy and fiber disarray of the Purkinge network
    - Early ventricular afterdepolarizations
  - Class IC agents and sotalol/dofetilide contraindicated
  - Definition of "significant" LVH debatable (>1.3-1.4 cm wall thickness)
  - Amiodarone only agent safe if "significant" LVH
- Absence of ischemia or LVH or systolic dysfunction
  - Propafanone or flecainide are good choices
- Renal insufficiency, prone to hypokalemia or bradycardia may increase risk of K-channel blockers (sotalol, dofetilide); avoid if GFR < 20
- Amiodarone prolongs QT but has very low risk of ventricular proarrhythmia
  - Extracardiac toxicity a serious issue

Kuboki. Jpn Heart J. 1999;40:233

Vernooy. Card Clin. 2004;22:21

Antiarrhythmic Choice Guided by Patient Specific Factors



Fuster. J Am Coll Cardiol 2006;48:854

Post-operative AF

- Oral beta-blocker is mainstay of therapy
- Preoperative amiodarone for those pts at high risk for developing post-operative atrial fibrillation
  - Cardiac surgery
  - Hx paroxysmal AF
  - HTN

WPW

- Long term: Catheter ablation is treatment of choice when associated with syncope or short refractory period of bypass tract
- Short term: IV Procainamide or Ibutilide to restore NSR in WPW pts with AF that is not hemodynamically significant; cardioversion if hemodynamically compromised
- **Avoid AV nodal blocking agents**
  - May precipitate fatal ventricular dysrhythmia

Hyperthyroidism

- Beta-blocker / correction of underlying disorder
- Non-dihidropyridine calcium channel antagonist (verapamil; diltiazem) when beta-blocker cannot be used
- Avoid amiodarone

Pregnancy

- No completely "safe" choice
- Most experience with beta-blocker (labetalol), nondihydropiridine calcium channel blocker, or digoxin

Hypertrophic Cardiomyopathy

- Tend to tolerate AF poorly due to diastolic dysfunction and importance of atrial kick
- Little evidence to guide pharmacologic choices
- Beta-blockers, nondihydropiridine calcium channel antagonists or amiodarone generally preferred; disopyramide has been used for gradient control and could be tried.

Pulmonary Disease

- COPD **NOT** an absolute contraindication to beta-blocker use
  - Bronchospastic lung disease is relative contraindication
- Non-dihydropiridine calcium channel blockers tend to be first line therapy
- Avoid amiodarone

Vaughan-Williams Classification of Antiarrhythmic Drugs

Type IA
- Disopyramide
- Procainamide
- Quinidine

Type IB
- Lidocaine
- Mexiletine

Type IC
- Flecainide
- Propafenone

Type II
- Beta blockers (e.g., propranolol)

Type III
- Amiodarone
- Bretylium
- Dofetilide
- Ibutilide
- Sotalol

Type IV
- Nondihydropyridine calcium channel antagonists (verapamil and diltiazem)

Fuster. J Am Coll Cardiol 2006;48:854

Class I Agents

- General Concepts
  - Sodium channel blocking potency
    - IC > IA > IB
    - Use dependency
      - Drug exhibits greater potency at higher heart rates
        - Proarrhythmia may be provoked by increased heart rate
        - Exercise testing following drug loading
    - Proarrhythmic impact of IC agents may be attenuated with use of beta-blockers

Quinidine

- Class IA
  - Associated with increased mortality
- Proarrhythmia
  - Dose-independent
  - QTc > 500 msec – decrease drug dose or discontinue
    - Pause dependent early after depolarizations
  - Alpha-adrenergic blocking property
    - Orthostatic hypotension
    - Reflex tachycardia
  - No negative inotropic effect
  - Vagolytic effect
    - May enhance AV nodal conduction and increase ventricular response rate
    - Use AV nodal blocking agent prior to starting quinidine
- No longer recommended in AF management guidelines due to poor patient tolerance (and risk of toxicity)

Proarrhythmia

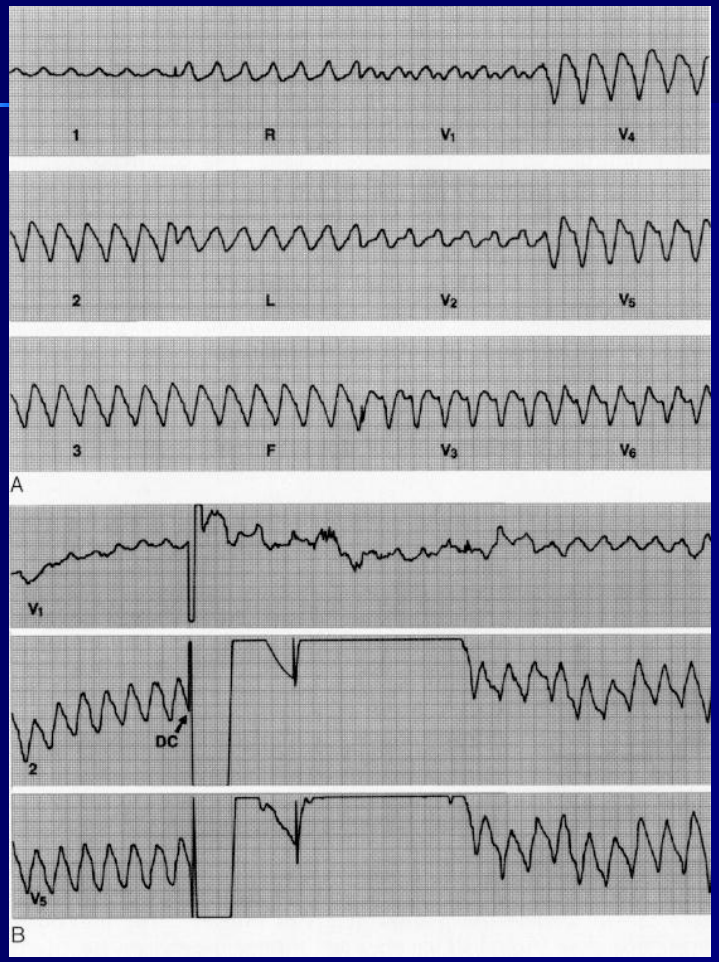
- Quinidine syncope
  - Most frequently due to polymorphic VT (0.5 to 4.4%)
  - VF
    - Median occurrence 3 days after initiation
- Avoid other class IA agents if TdP or VF is observed
- Initiate in hospital

Proarrhythmia

- Specific types of life-threatening proarrhythmia
  - New onset, sustained monomorphic VT
  - Increased frequency of sustained VT
  - Incessant VT
  - Torsade de Pointes
  - Drug induced cardiac arrest
  - Drug induced bradyarrhythmias
  - Atrial proarrhythmia: more frequent, more sustained, 1:1 flutter, digitalis -> AT with block [Berns, **Am J Cardiol 59:1337–1341, 1987)**

Kutalek, In Naccarelli GV (ed): Clinical Cardiovascular Therapeutics: Cardiac Arrhythmias… Futura, 1991

Class IC Proarrhythmia



Incessant VT in a patient on encainide. Cradioversion unsuccessful in converting to NSR

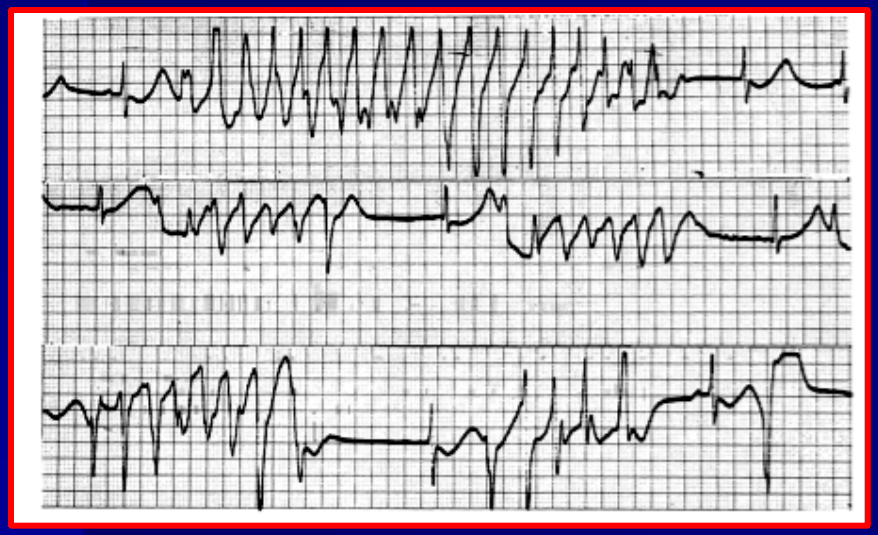
Quinidine Syncope

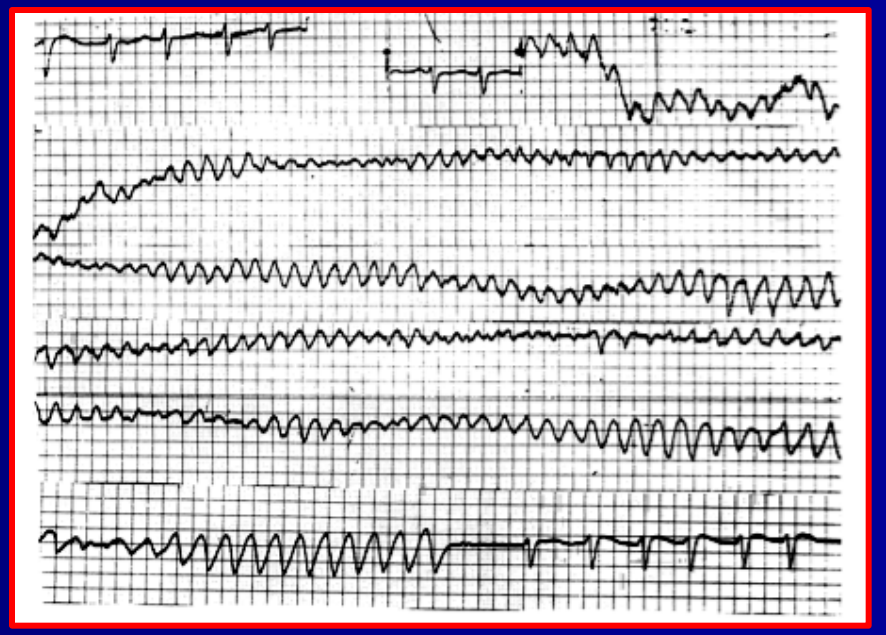
Paroxysmal Ventricular Fibrillation Occurring during Treatment of Chronic Atrial Arrhythmias

By Arthur Selzer, M.D., and H. Wesley Wray, M.D.

QUINIDINE occupies an almost unique place in the therapy of cardiac arrhythmias. In the 45-odd years of its clinical use only very few drugs possessing similar pharmacologic properties have been found, but none could match quinidine in its broad therapeutic applications. Consequently, the

First article demonstrating cause of "quinidine syncope to be PVT/self-terminating VF





Selzer. Circulation 1964;30:17

Quinidine

- Interactions with common CV drugs
  - Digoxin
    - Increased levels
      - Decreased tissue binding
      - Decreased renal and biliary clearance
      - Cut dose in ½
  - Warfarin
    - Anticoagulant effect increased
  - Heparin
    - Increases unbound fraction of quinidine
  - Verapamil
    - Increase quinidine levels by decreasing metabolism
  - Amiodarone
    - Increase quinidine levels
    - Increase impact on QT prolongation

Quinidine

- Side Effects
  - GI
    - Abdominal cramping
    - Diarrhea
  - Rash
  - Cinchonism (hearing decrease, tinnitus, blurred vision)
  - Thrombocytopenia
  - Coomb's positive hemolytic anemia
  - Lupus syndrome with anti-histone antibodies
  - Granulomatous hepatitis (rare)

Treatment of Proarrhythmia or Toxicity

- Infusion of sodium lactate or sodium bicarbonate
- Magnesium
- Isoproterenol
- Temporary pacing

Procainamide

- Class IA
- Used rarely for cardioversion
- Proarrhythmic potential
  - Increases when used with other drugs that prolong QT
- Hypotension during IV administration
  - Decreased sympathetic efferent activity
- Worsening CHF
  - Approximately 10%
- Amioadrone
  - Increases procainamide levels
- Active metabolite
  - NAPA
  - Class III effects
- No longer recommended in AF management guidelines due to poor patient tolerance (and risk of toxicity)

Procainamide

- Side Effects
  - GI – in 25% of patients
  - Rash
  - Fever
  - Raynaud's phenomenon
  - Agranulocytosis
  - Coomb's positive hemolytic anemia
  - Depression
  - Psychosis
  - Cholestatic jaundice
  - Drug induced lupus syndrome

Disopyramide

- Class IA
- Prolongs repolarization
  - May cause VF, TdP
  - Less than quinidine
- Marked negative inotropic effect
- Negative dromotropic effect
- Useful in patients with HOCM, vagally mediated AF (possibly)
- Drug interactions
  - Decreased plasma levels with
    - Phenobarbital, phenytoin, ripampin
  - Increased plasma levels with
    - Erythromycin
  - Negative inotropic effect can be additive with other negative inotropes
- No longer recommended in AF management guidelines due to poor patient tolerance (and risk of toxicity)

Disopyramide

- Side Effects
  - Anticholinergic – 30%
    - Dry mouth, blurred vision, constipation, urinary retention
      - Pyridostigmine can diminish the effect
  - Hypoglycemia
    - Enhanced secretion of insulin
  - Nausea
  - Vomiting
  - Rash
  - Cholestatic jaundice
  - Agranulocytosis (Conrad, JAMA 1978;240:1857)

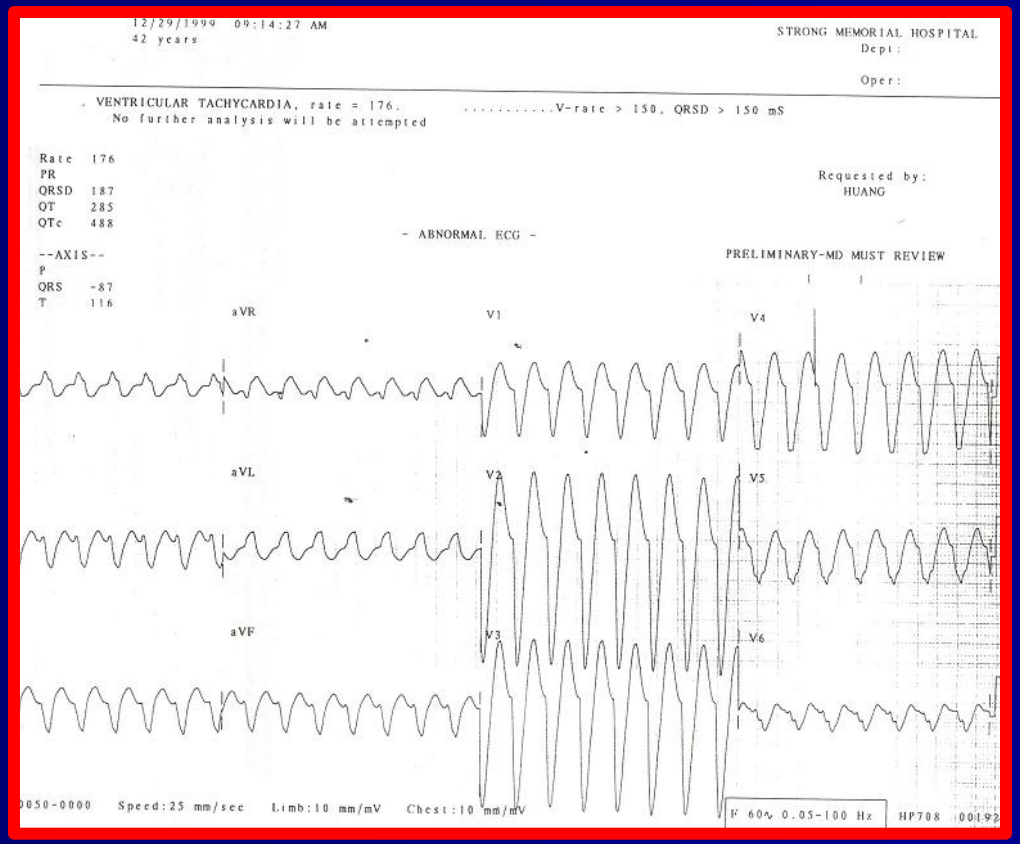
- ***Periodic CBC, LFTs may be prudent especially early after starting agent; frequency of testing not known; similarly with quinidine, procainamide.***

Flecainide

- Class IC
- Use dependence
  - Exercise testing recommended after achieving steady state
- Negative inotropic
  - May exacerbate CHF
- Beta-blockade used to treat proarrhythmia
  - Prevent 1:1 AV conduction

Pt on Flecainide with 1:1 Atrial Flutter

Flutter CL Slowed by Drug



Flecainide

- Drug Interactions
  - Digoxin
    - Levels increased 25% - decreased clearance
  - Amiodarone
    - Increased level
  - Quinidine
    - Inhibits hepatic metabolism
    - Increased elimination half-life 20%

Flecainide

- Side Effects
  - CNS effects
    - Blurred vision, headache, ataxia
  - CHF
    - Avoid with underlying LV systolic dysfunction (e.g., EF < 40%)

Propafenone

- Class IC
- Negative inotropic effect
  - In part due to beta adrenergic and calcium channel blocking activity
  - Up to 10% of those with LV dysfunction will have further exacerbation
  - Less pronounced than with flecainide or disopyramide

Propafanone

- Cytochrome P-450 2D6 enzyme
  - 7% of US population lack this enzyme
  - Responsible for metabolism of propafanone to 5 hydroxy-propafanone
  - Buildup of parent compound
    - More beta-blocking effect
- Drug Interactions
  - Digoxin levels increased > 80%
  - Warfarin clearance decreased
  - Theophylline, Cyclosporine, Disopyramide levels increased

Propafanone

- Side Effects
  - Nausea
  - Dizziness
  - Metallic taste
  - Exacerbation of asthma
  - CNS effects

Propafanone

- Proarrhythmia
  - Approximately 5% (in treatment of ventricular arrhythmias)
    - Rare in structurally normal heart
  - Treat with sodium lactate
  - AV nodal blocking agent to prevent 1:1 conduction

Class III agents

- Proarrhythmia often dose dependent
- QT prolongation and TdP
- Risk factors for TdP
  - Bradycardia
  - Baseline QT prolongation (≥450 msec)
  - Female gender
  - Hypokalemia
  - Hyopomagnesemia
  - Family history of congenital LQTS
  - Prior drug induced TdP
  - Multiple QT prolonging drugs or agents interfering with their metabolism
- Reverse use dependency (greater channel block at slower rate) -not true for amiodarone

Amiodarone

- Class III
  - Has beta and calcium channel blocking activities
  - Ejection fraction unchanged
  - Originally developed as an anti-anginal
- Less proarrhythmic but may still cause VF
- Multiple non-cardiac toxicities
- Drug interactions
  - Increases
    - Digoxin
    - Warfarin
    - Cyclosporin

Electrophysiologic Properties of Amiodarone

- Exhibits properties of all classes
  - Prolongs AP duration and refractory period
    - Class III
  - Decrease in phase 0 upstroke velocity
    - Class I
  - Non-competitive beta receptor blockade
    - Class II
  - Calcium channel blocking activity
    - Class IV

Kowey. AJC 1997;80:16G

Hohnloser. Ann Int Med 1994;121:529

Electrophysiologic Properties of Amiodarone

Actions of Intravenous Amiodarone vs Chronic Amiodarone

Actions	Intravenous Amiodarone	Chronic Amiodarone
Repolarization (QT interval) prolonged (atria and ventricles)	±	++++
Conduction velocity (atria and ventricles) reduced	++	++(as a function of rate)
Sinus rate reduced	+	+++
AV nodal conduction slowed	+	+
AV nodal refractoriness increased	++	+++
Atrial refractoriness increased	±	+++
Ventricular refractoriness increased	±	+++
Noncompetitive α- and β-blocking activity	+	++

+ = positive effect; ± = variable effect; ++ = moderate effect; +++ = large effect.

Singh. J Cardiovsc Electrophysiol 1999;10:283

Proarrhythmic Effects

- Incidence of proarrhythmia approximately 2% (TdP 0.7%)
- Mechanism for low incidence of TdP incompletely understood
  - Calcium channel blocking effects may reduce calcium dependant early afterdepolarizations necessary for initiation of TdP

Hohnloser. Ann Int Med 1994;121:529

Vorperian. JACC 1997;30:791

Amiodarone: QTc prolongation

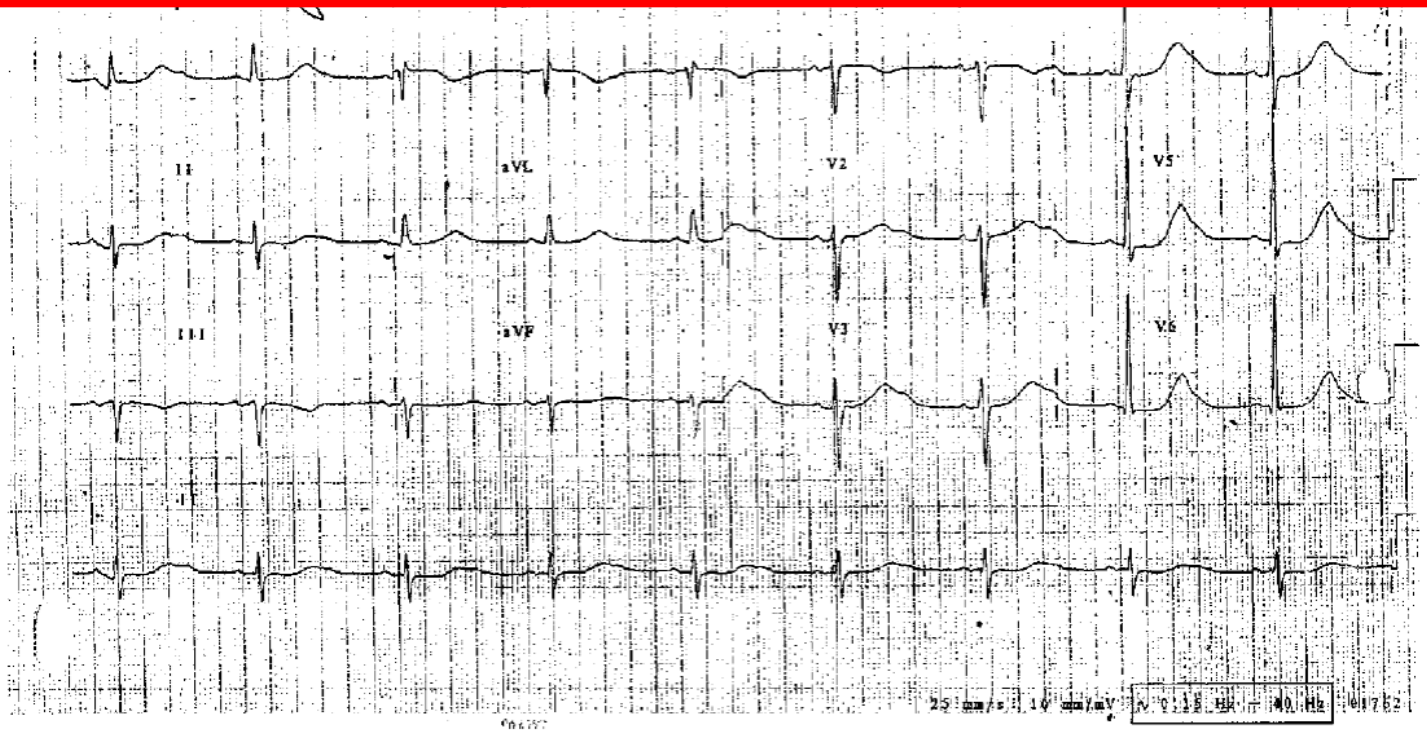


Figure 1. *ECG showing sinus bradycardia, QT 676 ms, QTc 660 ms, and QTd 140 ms while on a combination of azithromycin, amiodarone therapy.*

Reasons for Discontinuing Amiodarone in EMIAT

Reason for discontinuation	Placebo (n=743)	Amiodarone (n=743)
Endocrine disorders	12 (1·6%)	44 (5·9%)
Nervous-system disorders*	1 (0·1%)	4 (0·5%)
Gastrointestinal disorders	3 (0·4%)	10 (1·3%)
Hepatic disorders	2 (0·3%)	6 (0·8%)
Pulmonary disorders	3 (0·4%)	6 (0·8%)
Skin rash/ sensitivity	1 (0·1%)	9 (1·2%)
Vision disorders	1 (0·1%)	4 (0·4%)
Myocardial and valve disorders	13 (1·7%)	4 (0·5%)

Julian. Lancet 1997;349:667

EMIAT – Adverse Events

Adverse effects	Placebo (n=743)	Amiodarone (n=743)
Clinical hypothyroidism*	0 (0·0%)	11 (1·5%)
Clinical hyperthyroidism*	4 (0·5%)	12 (1·6%)
Gastrointestinal disorders	15 (2·0%)	22 (3·0%)
Nervous-system disorders*	8 (1·1%)	10 (1·3%)
Pulmonary disorders	30 (4·0%)	39 (5·2%)
Vision disorders	5 (0·7%)	5 (0·7%)
Skin disorders	0 (0·0%)	8 (1·1%)
Arrhythmia, except bradycardia	41 (5·5%)	23 (3·1%)
Bradycardia	1 (0·1%)	10)1·4%)
Liver disorders	6 (0·8%)	15 (2·0%)

*Cases assessed by Validation Committee. †Central and peripheral.

Julian. Lancet 1997;349:667

Increased non-cardiac mortality?

- Increased risk of pulmonary, cancer death in AFFIRM (majority treated with amiodarone)
- Non-cardiac mortality 37% higher in EMIAT vs. placebo (though non-statistically significant

TABLE 1. Mechanism of Death in the AFFIRM Study

Mode of Death	Rate Control (n=2027), n	Rhythm Control (n=2033), n	P*
Total deaths	310	356	0.07
Cardiac	130	129	0.95
Arrhythmic	79	77	0.88
Nonarrhythmic	43	46	0.75
CHF or shock, with MI	7	7	
CHF or shock, no MI	26	27	
Cardiac surgery/procedure	6	5	
Other/unknown	4	7	
Uncertain	8	6	0.60
Vascular	37	35	0.82
CNS	28	28	>0.99
Ischemic strokes	17	15	
CNS hemorrhage	11	13	
Other	9	7	
Noncardiovascular	113	169	0.0008
Pulmonary	23	39	0.04
Cancer	52	81	0.01
Other/uncertain	38	49	0.24
Unclassifiable	30	23	0.34

MI indicates myocardial infarction.
*Log rank test, unadjusted for multiple analyses.

Steinberg. Circulation 2004;109:1973

General recommendations for screening/follow-up

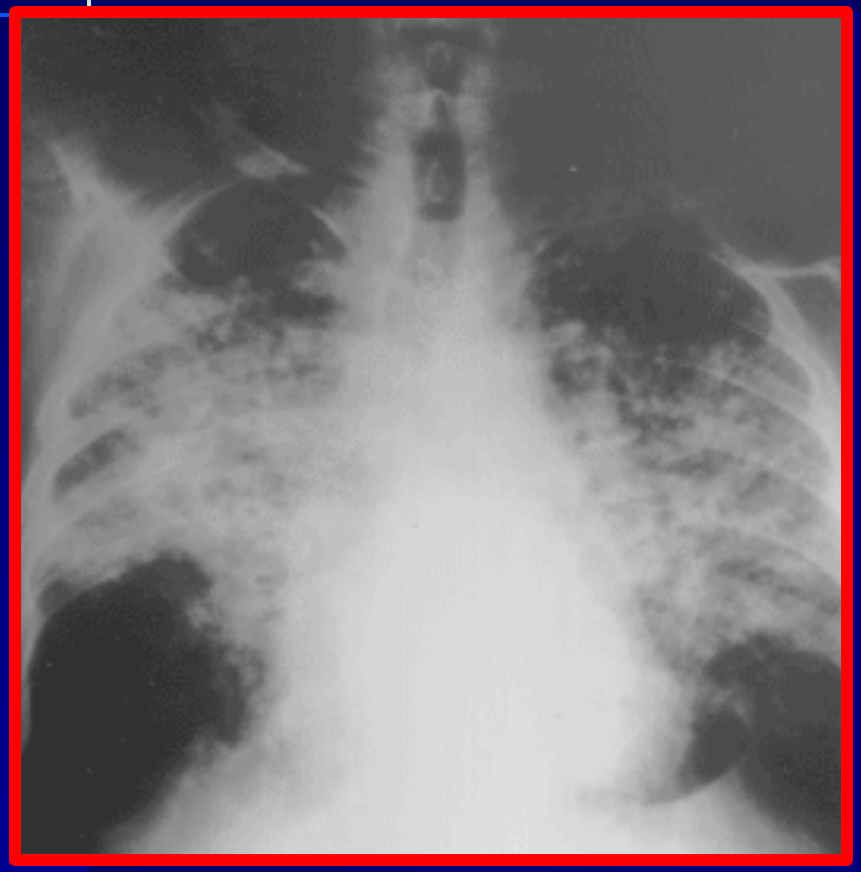
Non cardiac adverse effects of low-dose amiodarone maintenance therapy [46,48]

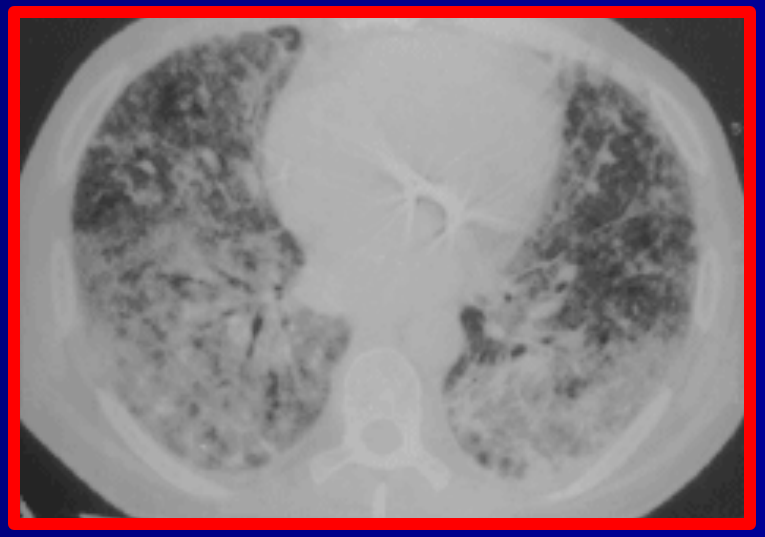
	Adverse effect (incidence)	Recommended screening/follow-up
Pulmonary	Hypersensitivity pneumonitis, and interstital pneumonitis/fibrosis (1% to 2%)	Radiograph at baseline and at least yearly, PFTs (with D_LCO) at baseline and as needed
Thyroid	Hypothyroidism (2% to 10%) hyperthyroidism (< 1%)	Baseline thyroid tests every 6 months and as needed
Gastrointestinal	Nausea, anorexia, constipation (up to 20%) AST/ALT ↑ > 2× normal (< 5%) hepatitis/cirrhosis (< 1%)	Baseline hepatic panel every 6 months and as needed; biopsy is suspected hepatitis or cirrhosis
Skin	Bluish discoloration (< 10%) photosensitivity, invariably in Caucasians	Baseline assessment of skin color/changes and as needed; recommend limited sun exposure and sun block
Ocular	Photophobia, corneal microdeposits (common) optic neuritis/irreversible blindness (< 1%)	Initial historical screening/exam and ophthalmology referral/slit lamp exam for baseline impairment and any visual changes as needed; corneal deposits rarely cause symptoms; discontinue if optic neuritis noted
Neurologic	Ataxia, peripheral neuropathy, memory/sleep problems (< 5%)	Baseline historical screening/exam and on follow-up; recommend dose reduction if symptoms/adverse effects noted
Genitourinary	Epididymitis, erectile dysfunction (< 1%)	Baseline historical screening and in follow-up as needed; symptoms may resolve or require dose reduction

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D_LCO, diffusing capacity of carbon monoxide; PFTs, pulmonary function tests.

Vernooy. Card Clin 2004;22:21

Amiodarone Lung Toxicity





University of Rochester Medical Center ISHNE Oct. 2007

Alonso-Fernandez. An Med Internat 2003;20(8)

Sotalol

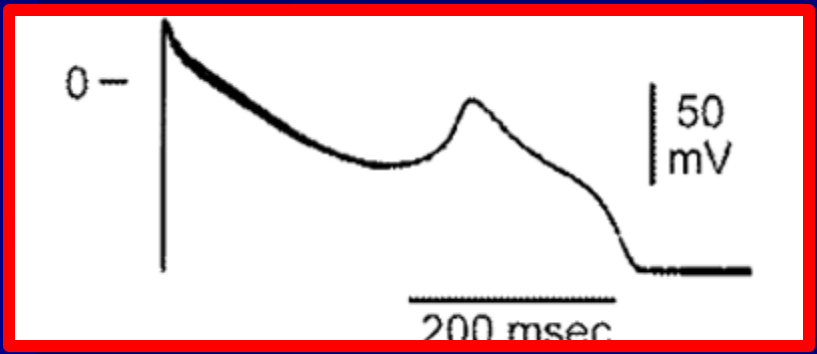
- Class III
- Potent beta-blockade
- Anti-hypertensive
- Exacerbate effects of other AV blocking drugs
- Side effects
  - Those of beta blockers
  - QT prolongation

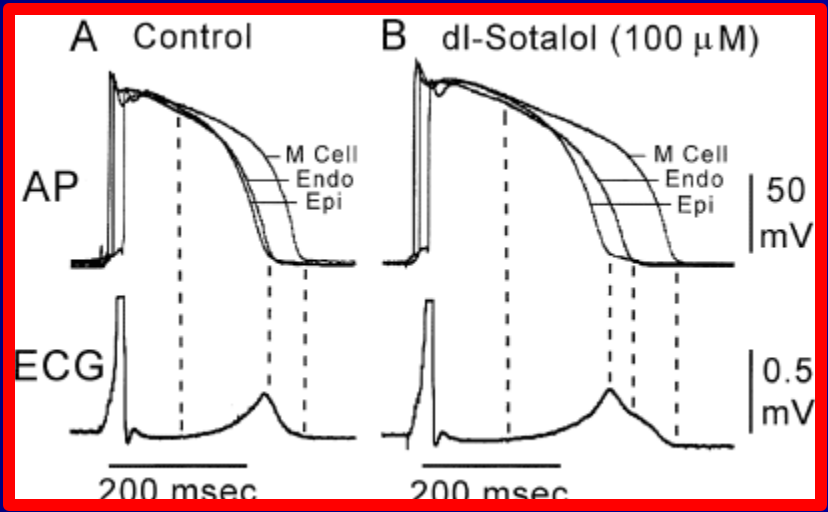
Sotalol

- Proarrhythmia
  - QT prolonging
    - Proarrhythmia in 3-5%
    - Particular attention in setting of
      - Hypokalemia
      - Hypomagnesemia
      - Higher dose ranges > 160 mg bid
  - D-sotalol
    - Pure I-Kr potassium channel blocker
    - SWORD trial
      - LV dysfunction and recent MI
      - Recent HF and remote MI
      - Use of D-sotalol associated with increased mortality

Sotalol

- Sotalol induced early afterdepolarization
- Sotalol induced QT prolongation





Fenichel. JCE 2004;15:475

Dofetilide

- Class III
- Pure IKr antagonist
- No negative inotropic properties
- Significant concern for proarrhythmia
  - Initiated in hospital – 6 doses
  - Follow QTc while loading
  - Contraindicated with CrCl < 20 mL/min
    - CrCl > 60 mL/min – 500 mcg BID
    - CrCl 40-60 mL/min – 250 mcg BID
    - CrCl 20-40 mL/min – 125 mcg BID
    - Reduce dose if QTc increases > 15% after 1st dose or QTc > 500 msec at any time
- DIAMOND
  - Risk of TdP 0.8% vs. 3.3% in DIAMOND-CHF
    - DIAMOND-CHF pts significantly more symptomatic, worse LV fxn, higher proportion of atrial fibrillation / flutter
  - 4 of 5 such events in first 3 days

Dofetilide

- All QT prolonging drugs must be stopped 3 days prior to initiation of Dofetilide; amiodarone longer (usually 30 d or more)
- Drug interactions
  - Cimetadine
  - Verapamil
  - Fluconazole
  - Trimethoprim
  - HCTZ
  - Amiodarone

Ibutilide

- Class III
- IV agent
- Proarrhythmia
  - Tdp – most common with imparied ventricular function and prolonged baseline QT interval
  - 4% with monotherapy
  - 1% after therapy with sodium channel blockers
    - Protective effect of IC agents
  - Women more susceptible to Tdp
    - 5.6% vs 3% in meta-analysis
- Avoid in low EF, heart failure
- Monitor at least 4 hours after dose / cardioversion
- Hypotension infrequent

"Pill-in-the-Pocket"

- Flecainide
  - 300 mg if >70 kg
  - 200 mg otherwise
- Propafanone
  - 600 mg if >70 kg
  - 450 mg otherwise
- Adverse effects in 12 outpatients (7 %)
- 1 atrial flutter with rapid rate
  - 11 non-cardiac side effects
- Risk stratified population
- Initial therapy inpatient with at least 8 hours monitoring
  - 14 (5%) symptomatic in the initial inpatient setting
    - 4 transient hypotension
    - 7 transient atrial flutter
    - 3 slightly symptomatic bradycardia

Alboni. NEJM 2004;351:2384-91

Beta-Blockers

- Adverse Cardiac Effects
  - Heart Failure
    - Exacerbation of decompensated heart failure
      - 6% with carvedilol
    - Precipitate heart failure in those with preexisting myocardial dysfunction
  - Negative chronotropic effects
    - Less prominent with drugs with ISA
      - Acebutolol, Pindolol
  - Beta-blocker withdrawal
    - Can lead to substantial morbidity or even mortality
    - Most likely with short acting beta-blockers such as propranolol

Beta-Blockers

- Adverse Non-Cardiac Effects
  - Increased airway resistance
    - Made worse especially with nonselective beta blockers
  - Exacerbation of peripheral arterial disease
    - Made worse especially with nonselective beta blockers
  - Facilitation of hypoglycemia
  - Hyperkalemia (typically <0.5 meq/L increase)
  - Depression
  - Fatigue
  - Sexual dysfunction
  - Numerous drug-drug interactions

Beta-Blocker Intoxication

- Clinical and Laboratory Features
  - Prominent features: hypotension and bradycardia
  - ECG can show PR prolongation and any bradyarrhythmia
  - Those with membrane stabilizing activity can show QRS prolongation
  - Mild hyperkalemia and hypoglycemia may be present

Beta-Blocker Intoxication

- Diagnostic Evaluation
  - Diagnosis depends on history and clinical presentation
  - Assays for beta blockers are not routinely available
  - Toxicologic differential diagnosis for unexplained bradycardia includes beta-blockers, calcium-channel blockers, digoxin, and cholinergic agents

Beta-Blocker Intoxication

- Management
  - ABC's
  - GI decontamination
  - Glucagon, 5 mg IV bolus, may be repeated if initial bolus has no effect
  - Calcium chloride (requires central venous access) or calcium gluconate IV
  - Vasopressors (usually norepinepherine)
  - Insulin and Glucose therapy
  - Consider temporary transvenous pacing, intraaortic balloon pump, and/or cardiopulmonary bypass

Calcium Channel Blockers

- With respect to atrial fibrillation
  - Non-dihydropyridine
    - Verapamil – constipation
    - Edema – mild
    - Diminished cardiac contractility and slowing of cardiac conduction
    - Possible increased risk in mortality hotly debated
      - Small increase in risk for acute MI in hypertensive patients
      - Possibly increased mortality, GI bleeding, and cancer in the elderly
      - Some studies failed to confirm increased risks (Kizer. Arch Int Med 2001;161:1145)

Calcium Channel Blocker Intoxication

- History and diagnostic evaluation similar to beta-blocker intoxication
- Treatment
  - IV fluids for hypotension
  - Atropine for bradycardia
  - Calcium Chloride (10-20 ml of 10% solution) or Calcium Gluconate (30-60 ml of 10% solution) followed by infusion (0.5 meq/kg/hr)
  - Glucogon
  - Vasopressors (norepinepherine)
  - Insulin, Glucose
  - GI decontamination
  - Consider tranvenous pacing, intraaortic balloon pump, Cardiopulmonary bypass, ECMO

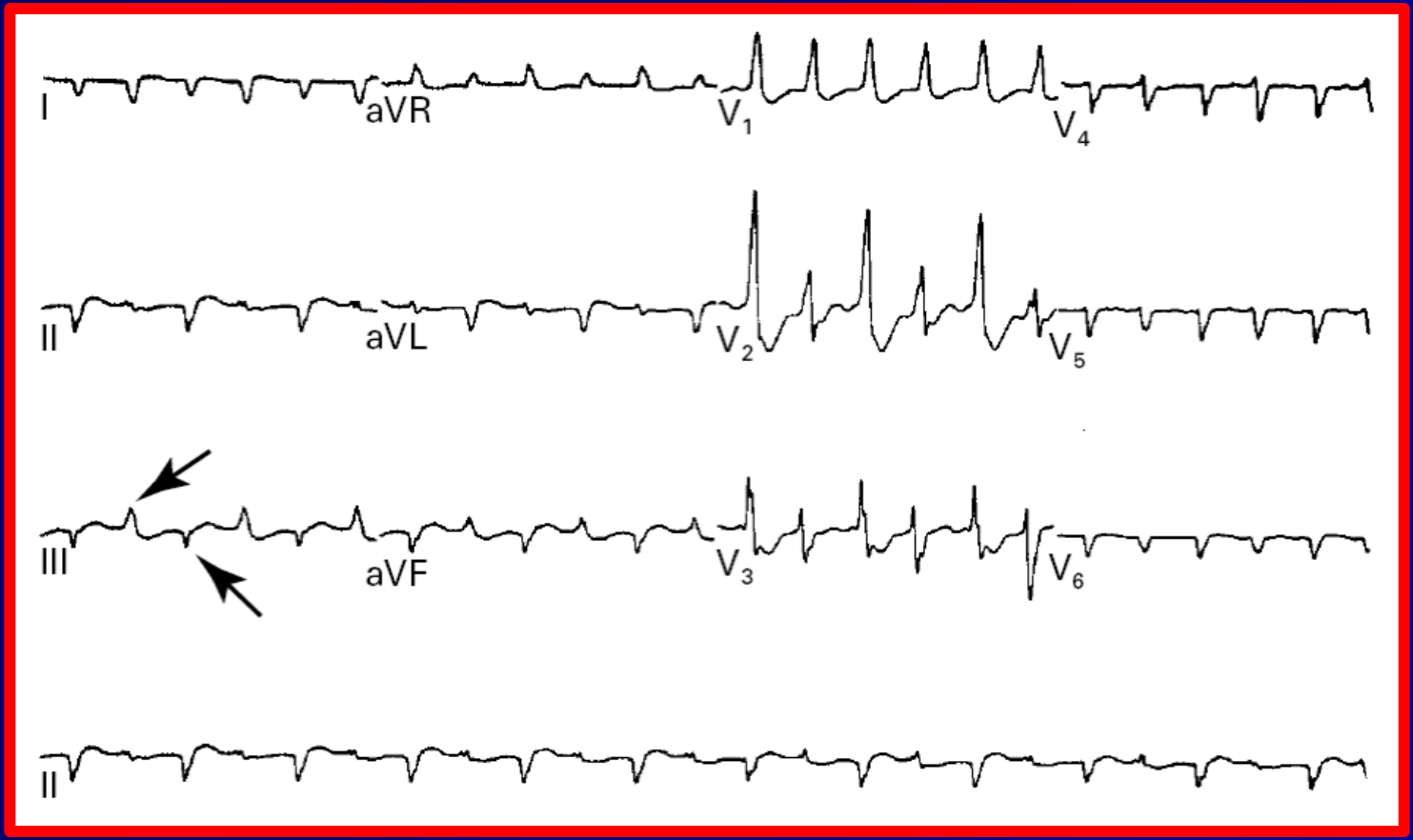
Digitalis

- Marked increased life threatening arrhythmias and other toxicities above serum levels of 2.0 ng/ml
- Signs of toxicity may occur at lower levels
- Hypokalemia can promote digitalis induced arrhythmias
- Maintain digoxin levels at lower range 0.5 – 0.8 ng/ml
- Measure levels at least 6 hours after last dose
- Concerns about increased risk of mortality
  - Dig study – No difference in mortality vs. placebo
    - substudy in women – possible increased risk however

Digitalis

- Mechanism of Arrhythmia
  - Delayed afterdepolarizations
  - Bradyarrhythmias due to enhanced vagal tone
- Ectopy/Arrhythmia
  - Ventricular premature beats
  - Bidirectional VT
  - AV junctional rhythms
  - Sinus bradycardia and SA block
  - AV block and AV dissociation
  - AFib or Flutter with a slow ventricular rate
  - Atrial tachycardia with AV block

Bidirectional VT



Valent. NEJM 1997;336:550

Digitalis Toxicity

- Treatment
  - ABC's
  - Symptomatic bradycardias
    - Atropine
    - Avoid pacing or isoproterenol – may precipitate arrhythmias
  - Hyperkalemia
    - Avoid treating with calcium
  - Hypokalemia and hypomagnesemia – mangage aggressively
  - Digoxin-specific Fab Fragments
    - Indications
      - Hemodynamic instability from digitalis toxicity
      - Life-threatening arrhythmias from digitalis toxicity
      - Severe bradycardia – even when responsive to atropine
      - Plasma potassium >5 meq/L in the setting of acute overdose regardless of clinical status or ECG findings
      - Plasma concentration >10 ng/mL regardless of clinical status or ECG findings
      - Ingestion of > 10mg of digoxin in adults or 4 mg in children
      - Presence of a digoxin-toxic rhythm in the setting of an elevated digoxin level

Hospital versus Outpatient Initiation

- Outpatient initiation avoided
  - Symptomatic sinus node dysfunction
  - AV conduction disturbance
  - Bundle branch block
  - Structural heart disease
  - QT prolongation
- In the absence of significant bradycardia and with normal ventricular function, QRS and QT intervals, proarrhythmia risk low

Hospital vs. Outpatient Initiation

- Propafenone and flecainide worsen AV nodal function (but slow AFL CL -> allow 1:1)
- Sotalol initiation as outpatient may be safe if QT < 440 msec in the absence of renal dysfunction and risk factors for TdP; however similar mechanism to dofetilide and possibly similar TdP risk; we favor inpt initiation (except in patients with an ICD)
- Start at lowest dose, titrate upward cautiously

Antiarrhythmic Monitoring

- Monitor PR interval
  - Flecainide
  - Propafenone
  - Sotalol
  - Amiodarone
- Monitor QRS
  - Flecainide
  - Propafenone
  - Amiodarone
- Monitor QT interval
  - Sotalol
  - Disopyramide
  - Dofetilide
  - Amiodarone
- Particular attention at rest (bradycardia prolongs the (uncorrected) QT)
  - QT prolonging agents (Sotalol, Dofetilide)
- Particular attention with exercise
  - IC agents

Measurement of QT Interval

- Avoid measuring QT interval on a technically inadequate tracing or concluding from single lead tracing that QT is not prolonged
- Hysteresis
  - Heart rate changes – QT interval changes
  - 1-2 minutes to reach new steady state
  - Analyze beats preceded by at least 2 minutes of stable rates
  - Discard analysis of beats during or just after heart rate changes

Moss. Am J Cardiol 1993;72:B23
Goldenberg. J Cardiovasc Electrophysiol. 2006;17:333

Measurement of QT Interval

- Different leads may give different results (QT dispersion)
  - Longest interval in any measurable lead
  - Interval measured with greatest precision
  - Lead II as a standard with V2 as second choice
  - Superimposition of different (up to all 12) digitally and simultaneously recorded leads

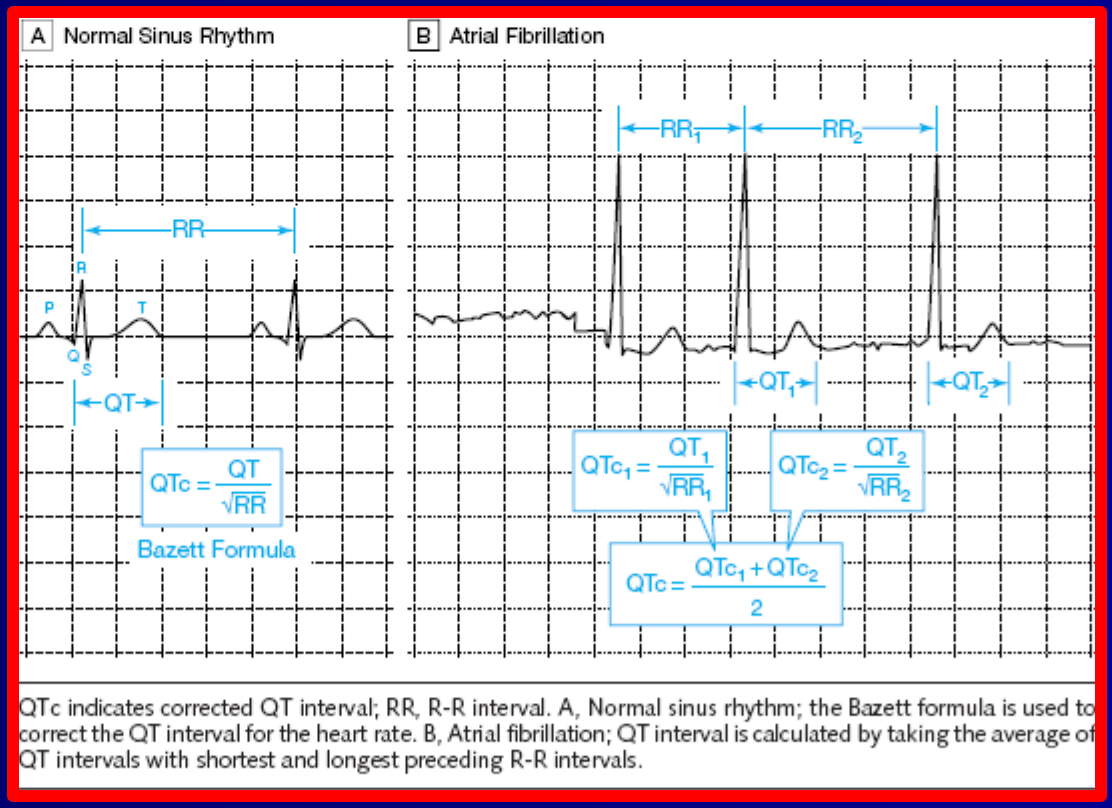
Measurement of QT Interval

- Do we include the U-wave
  - Small U-wave
    - Physiologic phenomenon
    - Not included in measurement
  - Large U-wave
    - "Notched T-wave"
    - T2-wave
    - Secondary part of repolarization pattern
    - Used in measurement

Correction of QT Interval measurement

- Bazett Formula
  - QT / (RR) $^{0.5}$
  - Derived empirically by prestatistical methods
  - Data from small population
  - Ease of computation
  - Upper limit of normal QT duration at a HR of 60 bpm (440 msec) probably is somewhat lower that the accepted upper limit
  - QT prolongation only mediocre predictor of Tdp or other ill effects

Measurement of QT Interval



QTc indicates corrected QT interval; RR, R-R interval. A, Normal sinus rhythm; the Bazett formula is used to correct the QT interval for the heart rate. B, Atrial fibrillation; QT interval is calculated by taking the average of QT intervals with shortest and longest preceding R-R intervals.

University of Rochester Medical Center ISHNE Oct. 2007

Al-Khatib. JAMA 2003;289:2120-7

Transmural Dispersion of Repolarization

- Differences in action potential durations between cells situated in different myocardial layers
- T wave peak
  - Termination of action potential from the epicardial layer
- T wave offset
  - Termination of repolarization in the M-cells

T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity

Masato YAMAGUCHI, Masami SHIMIZU, Hidekazu INO, Hidenobu TERAI, Katsuharu UCHIYAMA, Kotaro OE, Tomohito MABUCHI, Tetsuo KONNO, Tomoya KANEDA and Hiroshi MABUCHI

Molecular Genetics of Cardiovascular Disorders, Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, Takara-machi 13-1, Kanazawa 920-8640, Japan

Yamaguchi, Clinical Science 2003;105:671

Yamaguchi, et al.

- 27 patients with acquired LTQS
  - 12 with TdP
  - 15 without TdP
- QT Dispersion (QTD)
  - Difference between maximum and minimum QTc intervals
- Tpe (T peak-to-end interval)
  - T-wave peak-to-end interval divided by QTc interval in lead V5

Yamaguchi, et al.

Table 2 QT variables

Values are means (S.D.). T peak-to-end, peak-to-end interval of T wave in V5. NS, not significant.

QT variables	Group A	Group B	*P* value
RR interval (ms)	953 (244)	1004 (183)	NS
Maximum QT interval (ms)	631 (63)	504 (76)	0.0002
Minimum QT interval (ms)	512 (92)	445 (53)	0.0238
QTD (ms)	104 (52)	70 (41)	NS
Maximum QTc (ms)	657 (72)	505 (62)	< 0.0001
Minimum QTc (ms)	527 (55)	446 (37)	0.0001
QTDc (ms)	112 (64)	70 (40)	0.0456
T peak-to-end (ms)	185 (46)	84 (18)	< 0.0001
Tpe	0.337 (0.100)	0.187 (0.070)	0.0001

Yamaguchi, Clinical Science 2003;105:671

Yamaguchi, et al.

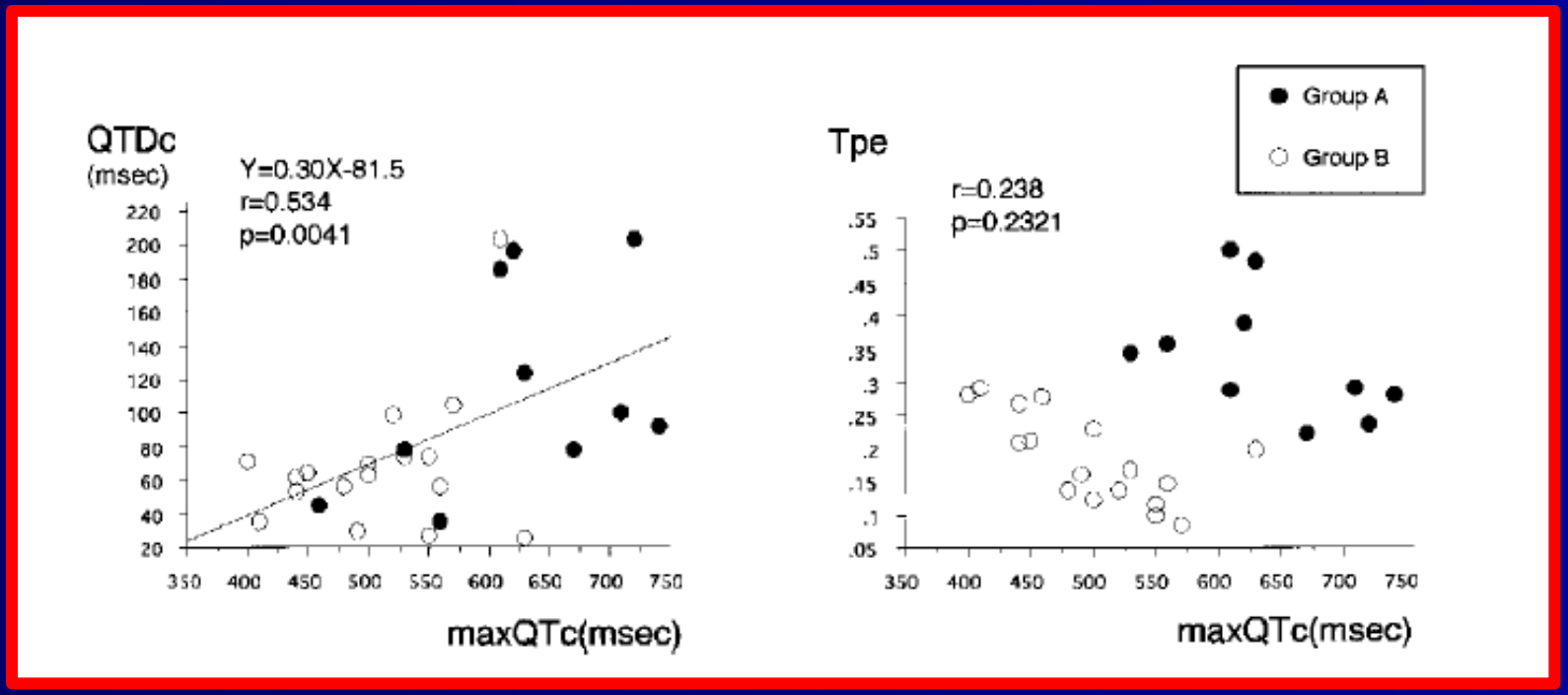
Table 3 **Univariate and multivariate logistic regression analysis**

OR, odds ratio; CI, confidence interval; NS, not significant.

	Univariate analysis			Multivariate analysis		
Variable	OR	95 % CI	*P* value	OR	95 % CI	*P* value
Age	1.014	0.940–1.094	NS			
Gender (male)	0.458	0.073–2.890	NS			
RR interval	0.999	0.995–1.003	NS			
Maximum QTc	1.022	1.008–1.037	0.0022	0.997	0.974–1.020	0.7751
Minimum QTc	1.037	1.010–1.065	0.0065	1.048	0.990–1.109	0.1079
QTDc	1.016	0.999–1.034	0.0666			
Tpe	2.388	0.929–4.077	0.0147	6.617	0.400–11.362	0.0552

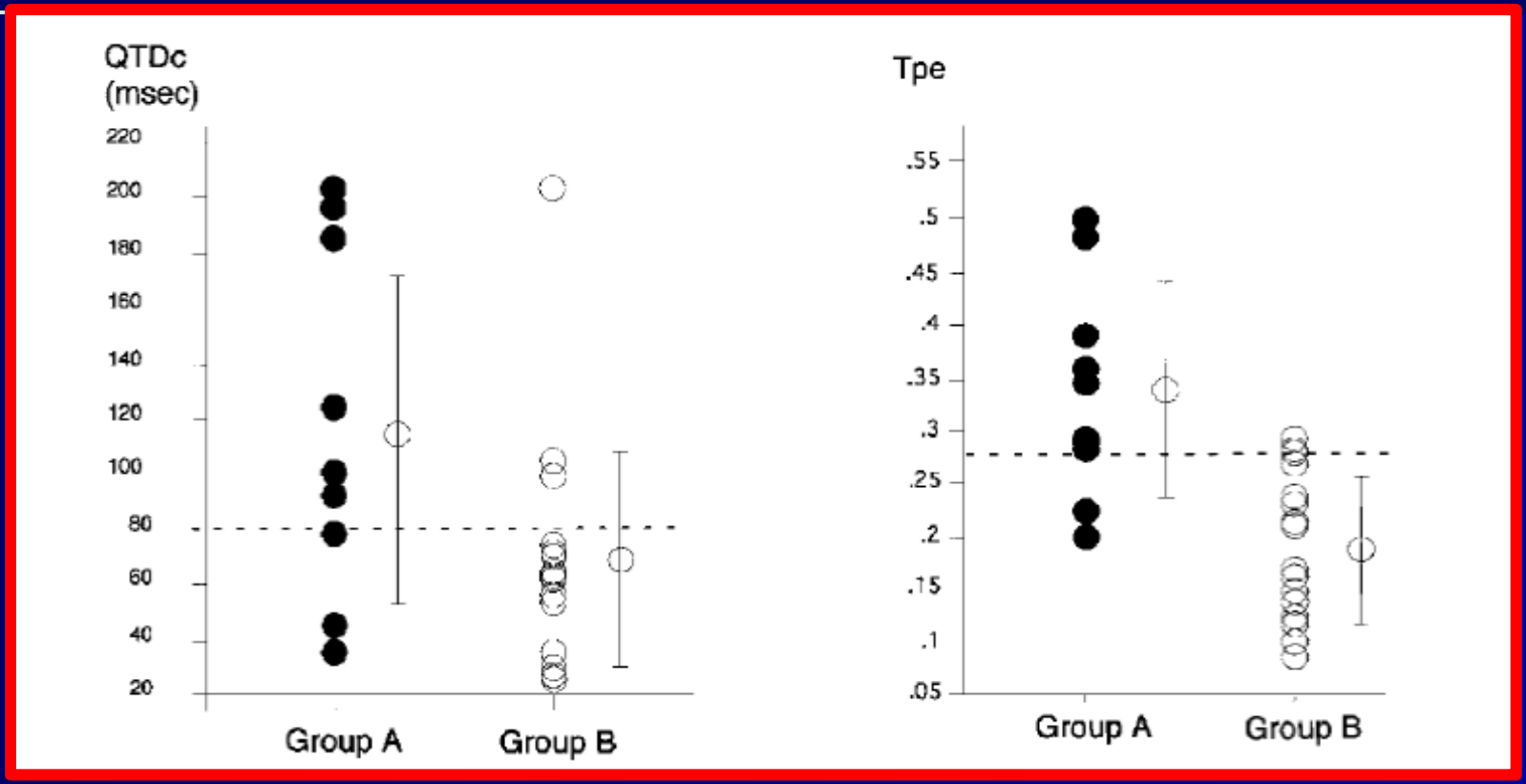
Yamaguchi, Clinical Science 2003;105:671

Yamaguchi, et al.



Yamaguchi, Clinical Science 2003;105:671

Yamaguchi, et al.



Yamaguchi, Clinical Science 2003;105:671

Yamaguchi, et al.

- Best predictor for TdP in the QT variables in patients with acquired LQTS was Tpe
- Tpe of 0.28 was a good cut-off point for TdP
- Tpe may be a more reliable indicator of TdP than QTDc in patients with acquired LQTS

Cellular Basis for Complex T Waves and Arrhythmic Activity Following Combined I_{Kr} and I_{Ks} Block

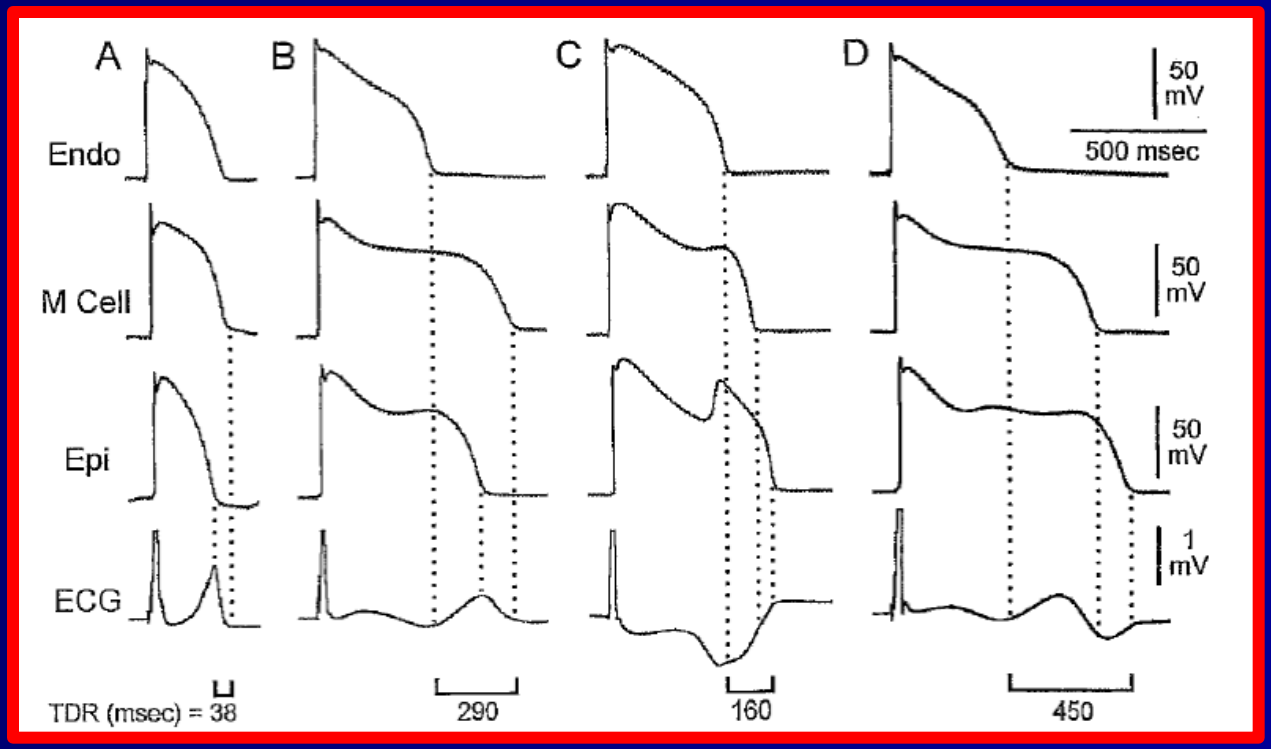
TETSURO EMORI, M.D., and CHARLES ANTZELEVITCH, PH.D.

From the Masonic Medical Research Laboratory, Utica, New York

Emori, J Cardiovasc Electrophysiol 2001;12:1369

Transmural Dispersion of Repolarization

Complex T-Wave Morphology



Emori, J Cardiovasc Electrophysiol 2001;12:1369

Transmural Dispersion of Repolarization

- Biphasic T-wave
  - Positive follows negative
  - $T_{nadir} - T_{end}$ = TDR
    - Dispersion greatest between enod- and M-cells
- Inverted T-wave
  - $T_{nadir} - T_{end}$ = TDR
    - Dispersion defined will be total epi- to endo-
    - Dispersion endo- to M- not easily extracted
- Triphasic T-wave
  - $T_{nadir(primary)} - T_{end}$ = TDR
    - Disperions defined will be total epi- to endo-
- Examples in setting of Ikr and Iks blockade with d-sotalol and chromanol 293B in a LV wedge preperation

Transmural Dispersion of Repolarization and Ventricular Tachyarrhythmias

Norikazu Watanabe, MD, Youichi Kobayashi, MD, PhD,
Kaoru Tanno, MD, PhD, Fumito Miyoshi, MD, Taku Asano, MD,
Mitsuharu Kawamura, MD, Yoshino Mikami, MD, Tarou Adachi, MD,
Syunsyou Ryu, MD, Akira Miyata, MD, PhD, and
Takashi Katagiri, MD, PhD

Watanabe, J Electrocardiolgy 2004;37:191

Watanabe, et al.

Table 1. Ventricular Tachycardia Detected in EPS

	VT Inducible group	VT Non-inducible Group	Control
N	37	25	65
Age	52.5 ± 16.9	56.2 ± 19.6	48.3 ± 18.1
Male/Female	32/5	16/9	31/34
Organic heart disease	26	10	5
Ejection Fraction(%)	52.4 ± 17.3	51.4 ± 16.9	61.6 ± 9.4

Watanabe, J Electrocardiolgy 2004;37:191

Watanabe, et al.

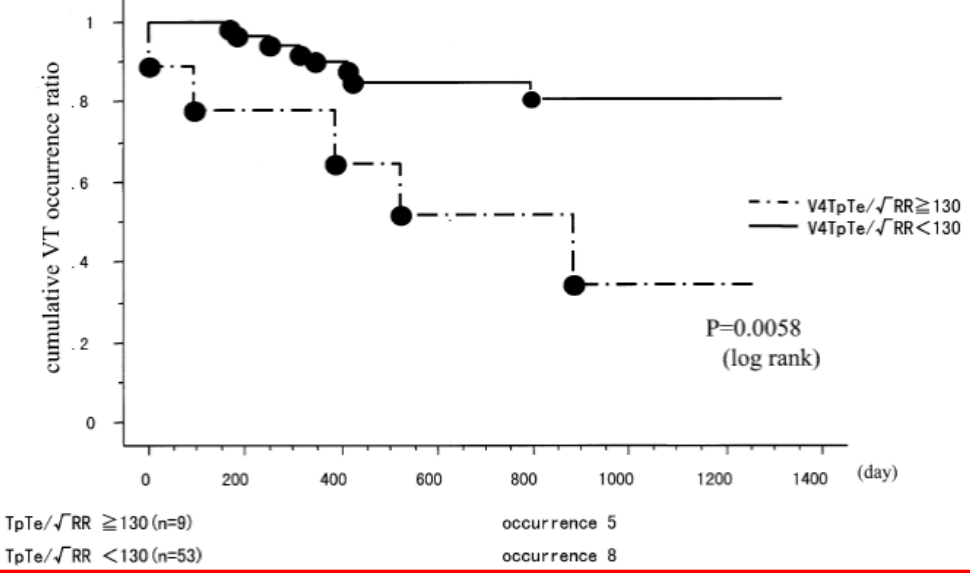


Table 4. V4TpTe ≠ √RR Values, Sensitivity, and Specificity

	V4TpTe/√RR≥130	V4TpTe/√RR<130
VT-occurrence	5	8
VT-non-occurrence	4	45

sensitivity 0.385
specicificity 0.918
positive predictive value 0.556
negative predictive value 0.883
P value .012 (χ^2 test)

Watanabe, J Electrocardiolgy 2004;37:191

Watanabe, et al.

- Prolonged TDR related to VT induction
- Prolonged TDR related to spontaneous occurrence of VT in high risk patients
- Might be a useful index to predict ventricular tachyarrhythmias

Watanabe, J Electrocardiolgy 2004;37:191

Drug-Induced Torsades de Pointes and Implications for Drug Development

ROBERT R. FENICHEL, M.D., PH.D.,[1] MAREK MALIK, PH.D., M.D.,[2]
CHARLES ANTZELEVITCH, PH.D.,[3] MICHAEL SANGUINETTI, PH.D.,[4]
DAN M. RODEN, M.D.,[5] SILVIA G. PRIORI, M.D., PH.D.,[6] JEREMY N. RUSKIN, M.D.,[7]
RAYMOND J. LIPICKY, M.D.,[8] and LOUIS R. CANTILENA, M.D., PH.D.,[9]
Independent Academic Task Force

- Mutations (<1% popluation)
- Polymorphisms (>1% population)
  - Widespread among human genes related to ion channels
- Certain subgroups
- May be clinically silent until exposed to a certain drug
- SCN5A S1102Y
  - 13/23 African Americans (57%) with Sustained arrhythmias (many drug induced) versus only 13% of 100 race-matched controls
- KCNE2 A116V
  Also implicated in cases of drug induced TdP

Mutations (in boldface), Polymorphisms, and Drug-Induced Torsades de Pointes

Gene	Coding Effect (Reference)	Drug	Remarks
KCNE2	T8A (20)	Quinidine	Allele frequency 1.6%
KCNE2	T8A (15)	Sulfamethoxazole/ trimethoprim	Allele frequency 1.6%
KCNE2	**Q9E** (20)	Clarithromycin	
KCNE2	**M54T** (15)	Procainamide	
KCNE2	**I57T** (15)	Oxatomide	
KCNE2	**A116V** (15)	Quinidine	
KCNH2	**P486R** (122)	Quinidine	
KCNH2	**R784W** (123)	Amiodarone	
KCNQ1	**Y315C** (124)	Cisapride	
KCNQ1	**R555C** (125)	Terfenadine (1) Disopyramide (1) Mefloquine (1) Diuretics (1)	**Three families, five events**
KCNQ1	**R583C** (123)	Dofetilide	
SCN5A	**G615E** (123)	Quinidine	
SCN5A	**L618F** (123)	Quinidine	
SCN5A	S1102Y (14)	Various drugs	Allele frequency among African-Americans 13%
SCN5A	**F1250L** (123)	Sotalol	
SCN5A	**V1667I** (126)	Halofantrine	**Four carriers with QT prolongation, one symptomatic with drug**
SCN5A	**L1825P** (126)	Cisapride	

Fenichel, J Cardiovasc Electrophysiol 2004;15:475

Torsades de Pointes

- Emergent Treatment
  - Magnesium
    - 2 gram bolus followed by an infusion of 2-4 mg/minute
  - Nonsynchronized cardioversion for hemodynamically unstable polymorphic VT or VF
  - Maintain serum potassium in high-normal range (4.5-5 mmol/L)
  - Discontinue QT prolonging medications or medications interfering with their metabolism
  - Overdrive transvenous pacing
    - 90 – 110 bpm typically used
  - Permanent pacemakers
    - Rates >70 bpm protective against drug induced TdP
  - Isoproterenol titrated to rate >90 bpm
    - Contraindicated with congenital LQTS or ischemic heart disease

Gupta. Am Heart J 2007;153:891-9

Torsades de Pointes

- Long-term Treatment
  - Avoidance of offending agents
  - Correct conditions predisposing to electrolyte abnormalities
  - Permanent pacing with pause prevention algorithms
    - Patients with
      - Sick sinus syndrome
      - AV nodal block and bradycardia
      - Pause dependent TdP

Gupta. Am Heart J 2007;153:891-9

In Summary…

- Safety is a concern when providing drug therapy for atrial fibrillation
- Patient factors must be evaluated
- Knowledge of drug classes and individual drugs, key interactions, and toxicities is paramount
- Limitations of QT prolongation as a marker for proarrhythmia
- Concept of transmural dispersion of repolarization
  - Measurement of $T_{peak} - T_{end}$
- Genetic predisposition for acquired LQTS
- Specific treatment of torsades de pointes