HealthCare
GILL HEART & VASCULAR INSTITUTE

Antiarrhythmic Drug Monitoring

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Financial Disclosures

- None

Background

Paradigm Shift: early rhythm control (antiarrhythmic drug therapy and ablation)

Increased risk of adverse effects and fatal arrhythmias if used incorrectly

Recommended monitoring parameters put forward to reduce risk of adverse effects

Background

Author (Year)	Setting	N	Compliance (%)
Sanoski et al. (1998)	Amiodarone Clinic*	60	**23**
Bickford et al. (2006)	Inpatient*	45	**11**
Raebel et al. (2006)	Ambulatory*	1,055	**53**
Snider et al. (2009)	Antiarrhythmic Medication Clinic^	134	**59**
Quaffa et al. (2017)	Pharmacy-Cardiology AAD Monitoring Program$^{\Delta}$	30	**70**
Kibert et al. (2019)	Pharmacy-Cardiology AAD Monitoring Program¥	40	**73**

*Amiodarone; ^Amiodarone, sotalol, dofetilide, propafenone; $^{\Delta}$Dofetilide; ¥Amiodarone, sotalol, dofetilide

Sanoski CA, *Pharmacotherapy*. 1998;18:146S-151S.
Bickford et al. *J Manag Care Pharm.* 2006;12:254-269.
Raebel MA, et al. *J Manag Care Pharm*. 2006;12(8):656-64.
Snider M, at al. *Clin Ther*. 2009; 31(6):1209-1218.
Quaffa LH, et al. *Ann Pharmacother*. 2017;51:39-43.
Kibert JL, et al. *J Am Coll Clin Pharm*. 2020;3:30-35.

Background

Spence et al. (2011)	Pharmacist Managed (%) N=181	Usual Care (%) N=2,111
Alanine Transaminase (ALT)		
Baseline	**84.0***	76.3
Months 1-12	**95.0***	87.1
Thyroid Stimulating Hormone (TSH)		
Baseline	**70.2***	62.7
Months 1-12	**93.9***	70.3
Chest Xray		
Baseline	**59.1***	49.3
Months 1-12	56.9	50.0
Pulmonary Function Test (PFT)		
Baseline	**6.6***	3.6
Months 1-12	**51.9***	14.0

*$p<0.05$

Antiarrhythmic Drug Monitoring

1. Selection of agents to monitor
   - Flecainide, propafenone, amiodarone, propafenone, sotalol, dofetilide

2. Identification of monitoring parameters and frequency of follow up
   - E.g., LFTs, TSH, CXR, CMP, BMP, magnesium

3. Defining criteria which requires further evaluation or intervention
   - I.e., out of range or overdue

Flecainide

Pharmacokinetics:

- Metabolism: Liver (CYP2D6 major)
- Elimination: 30% in urine as unchanged drug
- $T_{1/2}$: 20 hours (12-27)
- Steady state: 3-5 days

Effect on ECG: prolongation of PR and QRS intervals

- Electrolytes: Potassium and Magnesium

FLECAINIDE ACETATE (flecainide)[package insert]. Jacksonville, FL; Ranbaxy; Revised January, 2012.
Flecainide. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept.7, 2022.

Propafenone

Pharmacokinetics:

- Metabolism: Liver (CYP2D6 major, CYP3A4 major)
- Elimination: ~50% of propafenone metabolites are excreted in urine
- $T_{1/2}$: 2 – 10 hours
- Steady state: 4-5 days

Effect on ECG: prolongation of PR and QRS intervals

- Electrolytes: Potassium and Magnesium

RYTHMOL (propafenone)[package insert]. Whippany, NJ; Ranbaxy; Revised March, 2013.
Propafenone. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Flecainide & Propafenone Monitoring

Recommended Test	Monitoring Frequency
ECG	**Baseline, q 6 months**
CMP: Liver function, K+	**Baseline, q 6 months**
Magnesium	**Baseline, q 6 months**

<u>Adjustments based on ECG</u>

QRS increases on average ~25%;

>25% considered proarrhythmic

Amiodarone

Pharmacokinetics:

- Metabolism: Liver (CYP3A4 major)
- $T_{1/2}$: 58 days (15-142)
- Steady state: 265 days (130-535) without load dose
- Volume of distribution: ~60 L/kg

Effect on ECG: Prolongation of PR and QT (~10%)

- Electrolytes: Potassium and Magnesium

CORDARONE (amiodarone)[package insert]. Ambares, France; Sanofi; Revised October, 2018.
Amiodarone. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Amiodarone

Adverse Event	Incidence (%)
Hypothyroidism	4-22
Hyperthyroidism	2-12
Pulmonary Toxicity	2
GI: Nausea/constipation	~25
GI: AST/ALT elevation; hepatitis	15-30; <2
CNS (ataxia, neuropathy, tremor, sleep disturbance)	3-30
Skin: Blue - gray discoloration	<10
Skin: Photosensitivity	~15
Ocular: Optic neuropathy	<1
Ocular: Halos around lights	<5
Ocular: visual blurring, corneal deposits	> 90

Goldschlager N, et al. Heart Rhythm 2007; 4:1250-1259
CORDARONE (amiodarone)[package insert]. Ambares, France; Sanofi; Revised October, 2018.

Amiodarone Monitoring

Recommended Test	Monitoring Frequency
ECG	**Baseline, q 6 months**
CMP: K+ and **LFTs**	**Baseline, q 6 months**
Magnesium	**Baseline, q 6 months**
Thyroid Function Test	**Baseline, q 6 months**
Chest X-ray	**Baseline, q 12 months**
Pulmonary Function Test – with diffusion capacity	**Baseline,** with symptoms
Ophthalmic Exam	Baseline if visual impairment, with symptoms

Drug – Drug Interactions

Inhibits: CYP3A4 (moderate), 2C9, 2D6, OCT2, and Pgp

Goldschlager N, et al. Heart Rhythm 2007; 4:1250-1259
CORDARONE (amiodarone)[package insert]. Ambares, France; Sanofi; Revised October, 2018.

Dronedarone

Pharmacokinetics:

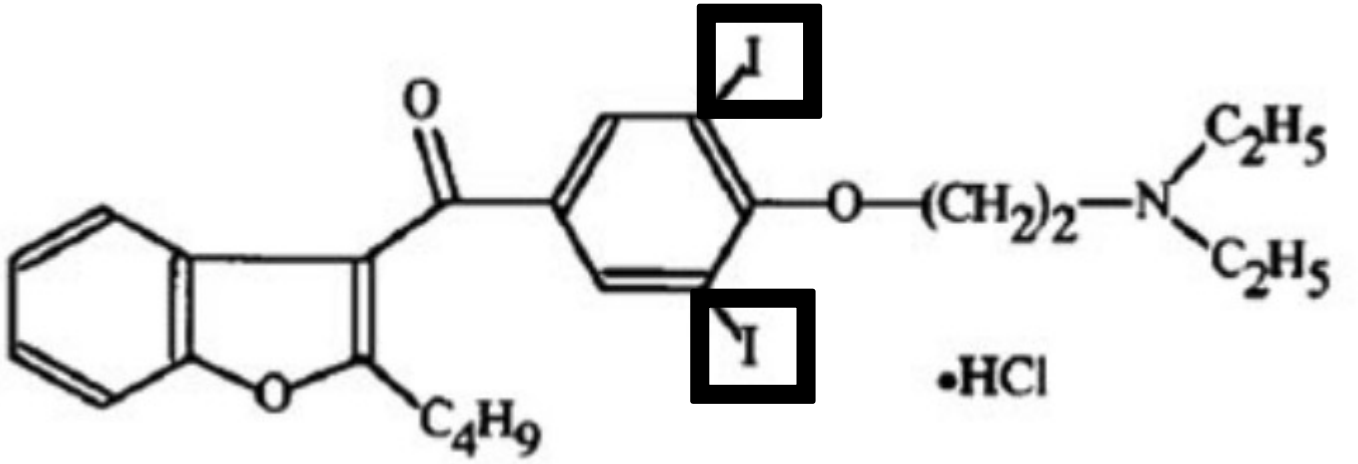
- Absorption: ~4% (extensive first pass metabolism); ↑ 15% with **high fat meal**
- Metabolism: Liver (CYP3A4 major)
- $T_{1/2}$: 13-19 hours
- Steady state: 4-8 days

Effect on ECG: Increase in PR (~5 msec) and QTc interval (~10 msec)

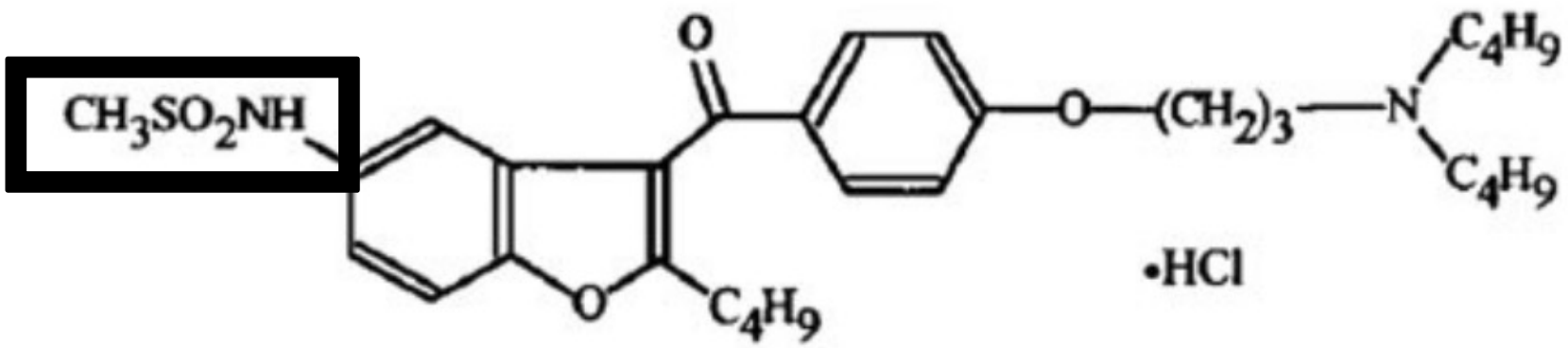
- Electrolytes: Potassium and Magnesium

MULTAQ (dronedarone)[package insert]. Bridgewater, NJ; Sanofi; Revised November, 2020.

Amiodarone



Dronedarone



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

Dronedarone Monitoring

Recommended Test	Monitoring Frequency
ECG*	**Baseline, q 6 months**
CMP: Scr, K+, and ^liver function	**Baseline, q 6 months**
Magnesium	**Baseline, q 6 months**

* Package insert recommends every 3 months
^ Recommended within the first 6 months, unknown if periodic monitoring will prevent liver injury; contraindicated in patients with severe liver impairment

Adjustments based on ECG

Maintenance: contraindicated if QTc ≥ 500 msec

Discontinue if in permanent AF

Drug – Drug Interactions

Inhibits: CYP3A4 (moderate) and P-gp

MULTAQ (dronedarone)[package insert]. Bridgewater, NJ; Sanofi; Revised November, 2020.

Sotalol

Pharmacokinetics:

- Metabolism: N/A
- Elimination: Kidney
- $T_{1/2}$: 12 hours
- Steady state: 2-3 days

Effect on ECG: Prolongation of QT and risk for Torsade de Pointes

- Directly related to plasma concentration
- Electrolytes: Potassium and Magnesium

BETAPACE AF (sotalol HCL) [package insert]. Switzerland; Covis; Revised May, 2016.
Sotalol. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Sotalol Monitoring

Recommended Test	Monitoring Frequency
ECG	**Baseline, q 6 months**
BMP: for Scr (CrCL) and K+	**Baseline, q 6 months**
Magnesium	**Baseline, q 6 months**

Dose adjustments based on estimated CrCl

AF/AFL

(calculated with Cockcroft-Gault)

- >60: twice daily
- 40-60: daily
- <40: contraindicated

Adjustments based on ECG

Maintenance: contraindicated if QTc >520 msec

BETAPACE AF (sotalol HCL) [package insert]. Switzerland; Covis; Revised May, 2016.
Sotalol. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Dofetilide

Pharmacokinetics:

- Metabolism: CYP3A4
- Elimination: Kidney with 80% excreted as unchanged drug
- $T_{1/2}$: 10 hours
- Steady state 2-3 days

Effect on ECG: Prolongation of QT and risk for Torsade de Pointes

- Directly related to plasma concentration
- Electrolytes: Potassium and Magnesium

TIKOSYN (dofetilide) [package insert]. Ney York, NY; Pfizer; Revised August, 2019.
Dofetilide. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Dofetilide Monitoring

Recommended Test	Monitoring Frequency
ECG*	**Baseline, q 6 months**
BMP*: for Scr (CrCL) and K+	**Baseline, q 6 months**
Magnesium	**Baseline, q 6 months**

*Package insert: every 3 months or medically warranted

Dose adjustments based on estimated CrCl

(calculated with Cockcroft-Gault)

- >60: 500 mcg BID
- 40-60: 250 mcg BID
- 20-39: 125 mcg BID
- <20: contraindicated

Adjustments based on ECG

Maintenance: contraindicated if QTc >500 msec (550 with ventricular conduction abnormalities)

TIKOSYN (dofetilide) [package insert]. Ney York, NY; Pfizer; Revised August, 2019.
Dofetilide. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Dofetilide Monitoring

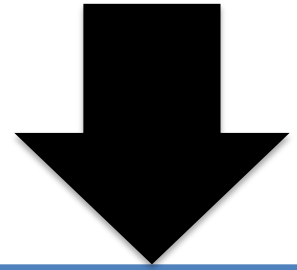
Drug – Drug Interactions

Contraindicated medications

- Cimetidine
- Verapamil
- Hydrochlorothiazide
- Trimethoprim
- Prochlorperazine
- Megestrol
- Ketoconazole
- Dolutegravir

TIKOSYN (dofetilide) [package insert]. Ney York, NY; Pfizer; Revised August, 2019.
Dofetilide. Drug Information. Lexicomp. Wolters Kluwer. Hudson, OH. Available at https://online.lexi.com. Accessed Sept 7, 2022.

Application To Practice

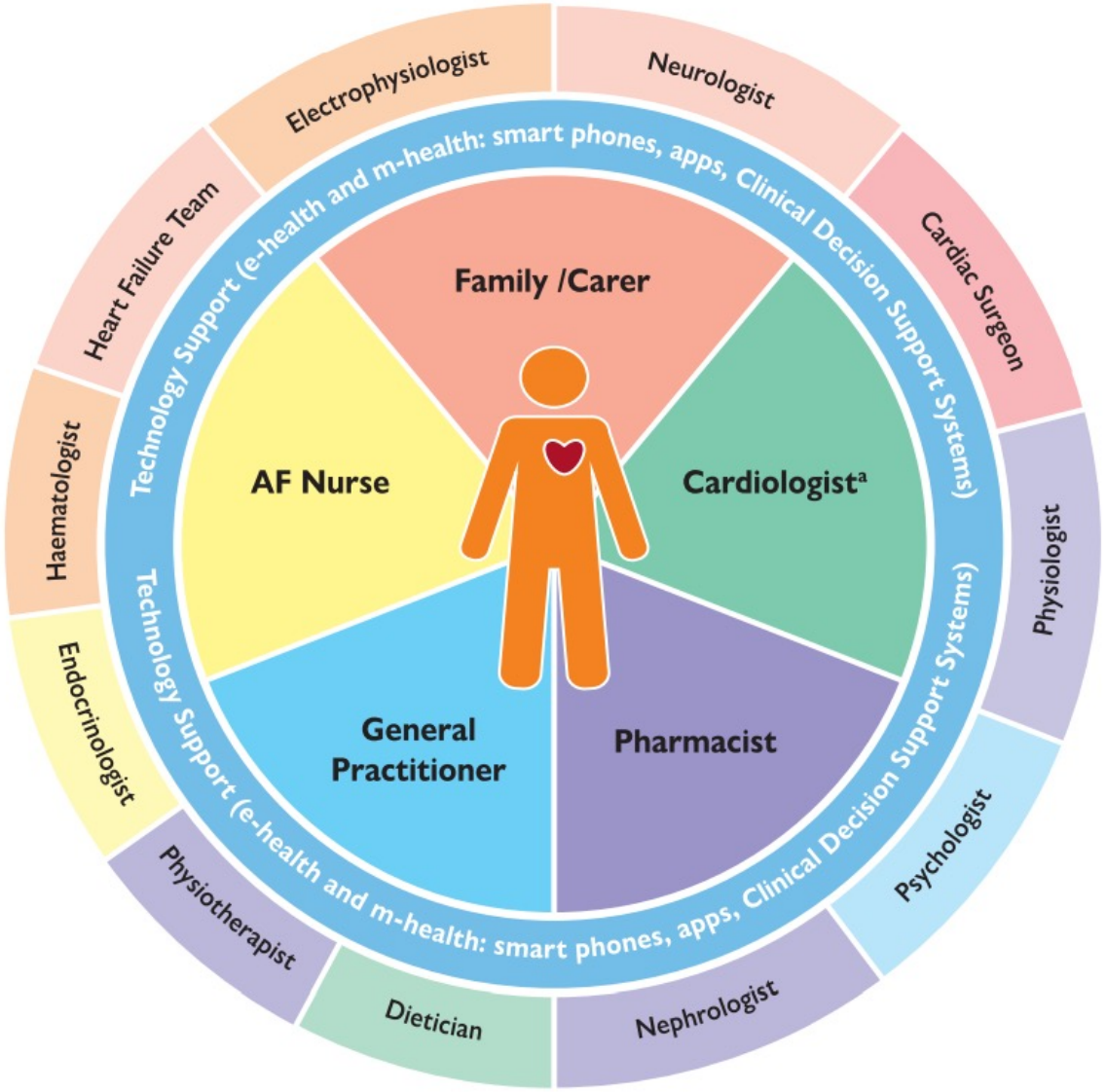


Author (Year)	Setting	Compliance (%)	After Enrollment Compliance (%)
Sanoski et al. (1998)	Multidisciplinary Amiodarone Clinic	23	**90***
Snider et al. (2009)	Antiarrhythmic Medication Clinic	59	**99***
Quaffa et al. (2017)	Pharmacy-cardiology AAD Monitoring Program	70	**99***
Kibert et al. (2019)	Pharmacy-Cardiology AAD Monitoring Program	73	**94***

*p=<0.05

Sanoski CA, *Pharmacotherapy*. 1998;18:146S-151S.
Snider M, at al. *Clin Ther*. 2009; 31(6):1209-1218.
Quaffa LH, et al. *Ann Pharmacother*. 2017;51:39-43.
Kibert JL, et al. *J Am Coll Clin Pharm*. 2020;3:30-35.

Interdisciplinary Team Approach



Patient

Electrophysiologist/Cardiologist

General Practitioner

Pharmacist

EP Nurse

Takeaways

- Prospective monitoring of AAD can improve compliance with monitoring parameters
- Development and incorporation of defined monitoring parameters into practice can help reduce risk of adverse events associated with AAD