Antiarrhythmic Drugs and Proarrhythmia – Case Based Discussions

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Disclosures: Consultant – Novartis, Celgene. Daiichi-Sankyo, Milestone

Proposed Definitions for Proarrhythmia

- Manifest -directly relatable to known electrophysiologic action of the agent with characteristic ECG findings
  - Dose related
  - Inherited or acquired disease influenced
  - Situational – transient factors

- Hidden – increased mortality seen in large populations without documentation of typical ECG phenomena

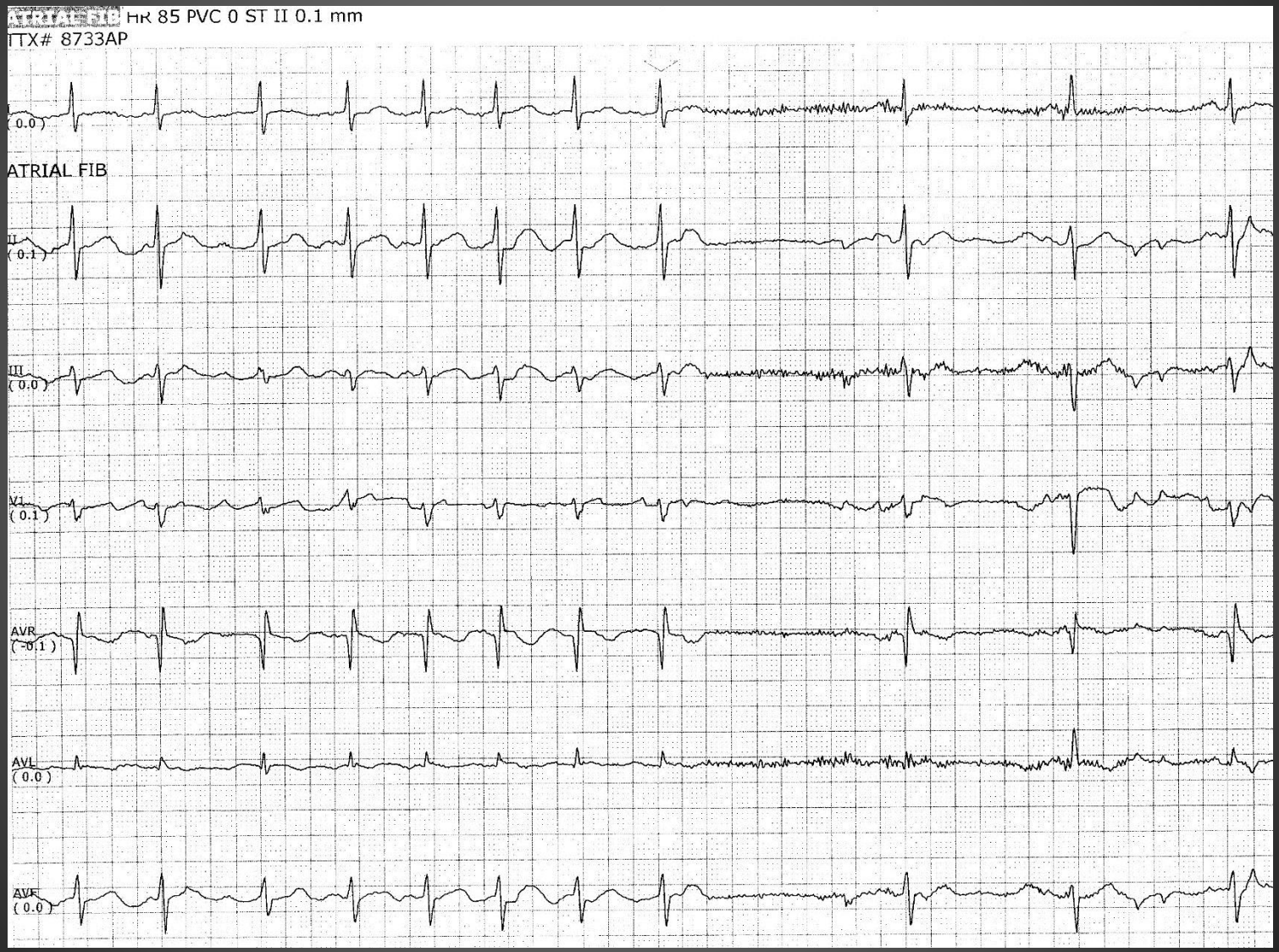
Case 1

A 57 year old man with hypertension and single vessel CAD developed atrial fibrillation 3 years ago. He was anticoagulated, hospitalized and converted to sinus rhythm after 3 doses of dofetilide, 500 μg every 12 hours. He has been maintained on dofetilide since without any known AF recurrence. Other medications are lisinopril, metoprolol and apixaban.

During a recent prolonged vacation in Costa Rica, he was found to be HIV positive. He was begun on bictegravir[1]-emtricitabine[2]-tenofovir alafenamide[2] (Biktarvy) as initial antiviral therapy.

1 - integrase strand transfer inhibitor (INSTI)
2 – nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)

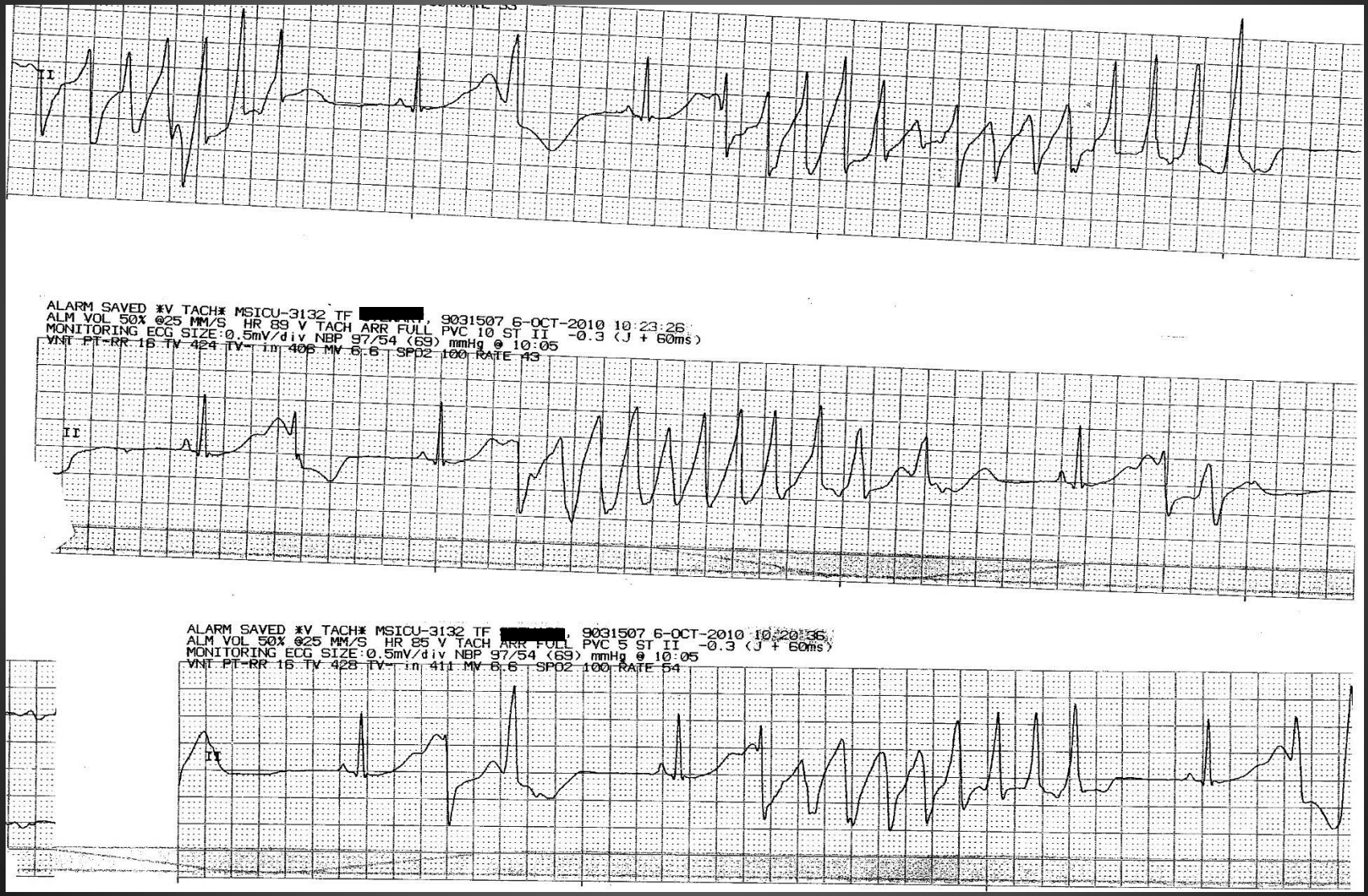
Dofetilide Conversion



Case 1

He returned home last week. Due to some back pains he started taking ibuprofen, 400 mg 3-4 X a day. Today he had a syncopal episode, striking his head during the fall. He was brought to the ER. His initial heart rate was 60 with a measured QT interval of 600 msec. Electrolytes were normal with a creatinine of 1.2 mg/dl. A head CT was normal. A rhythm strip captured on telemetry after admission is shown on the next slide.

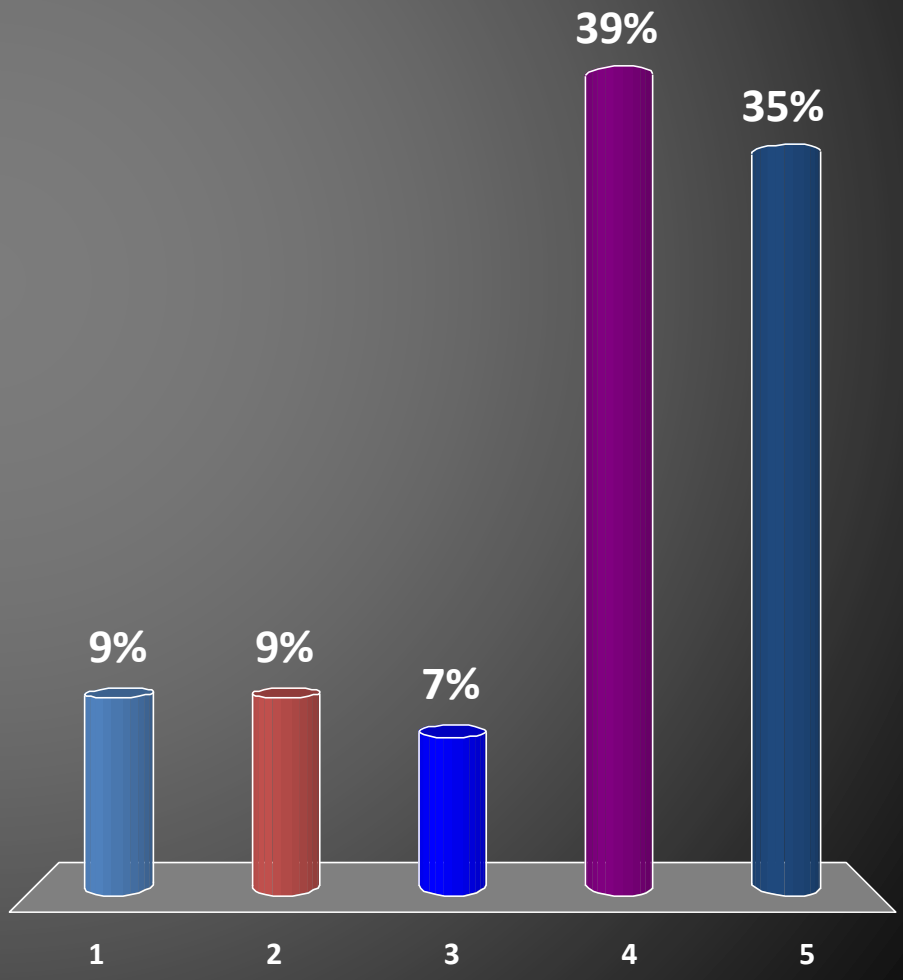
Case 1 - Telemetry



Question 1

Which of the following drugs are probable contributors to this syndrome:

1. Dofetilide
2. Biktarvy
3. Ibuprofen
4. 1 and 2
5. 1, 2 and 3



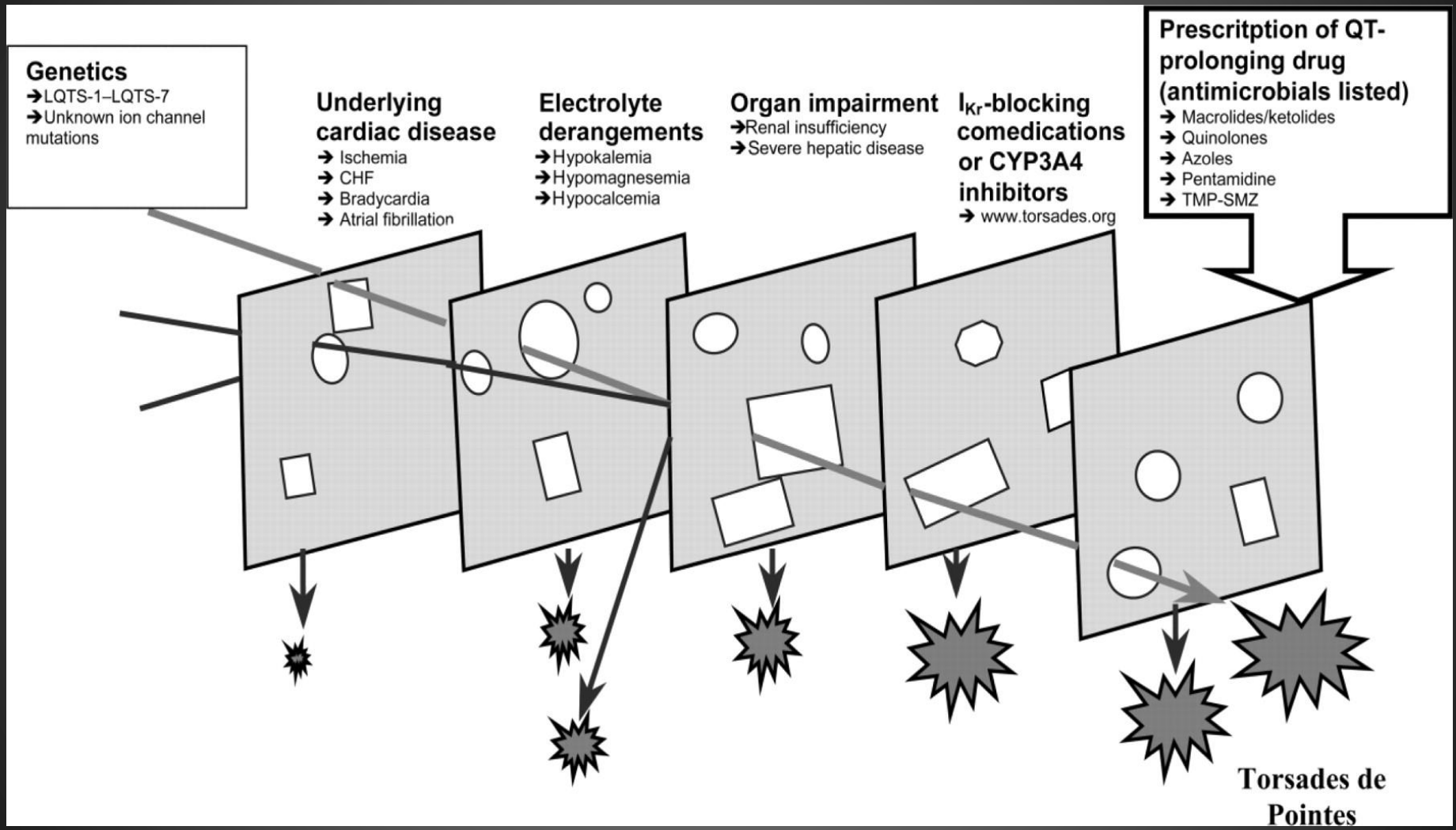
Risk Factors for Proarrhythmia

Table 2 Common clinical risk factors for drug-induced QT prolongation and Torsades de Pointes

- Female gender
- Conditions predisposing to heightened QT prolongation and risk of arrhythmia
  - Heart disease
    - Congestive heart failure
    - Left-ventricular hypertrophy
    - Hours following conversion of atrial fibrillation to sinus rhythm
  - Congenital long-QT syndrome (may be clinically unrecognized)
  - Bradycardia and conduction disease
- Increased drug bioavailability
  - Altered function of specific cytochrome P450 (CYP450) isoforms (for liver metabolized drugs) Genetic variants
    - Concomitant inhibitory drugs
    - Liver disease
    - Altered renal or liver function (for renally or hepatically excreted drugs)
- Electrolyte imbalance
  - Hypokalaemia
  - Hypomagnesaemia
  - Hypocalcaemia (possible)

Behr and Roden. Euro Heart J 2013;34:89-95.

Preventing Proarrhythmia

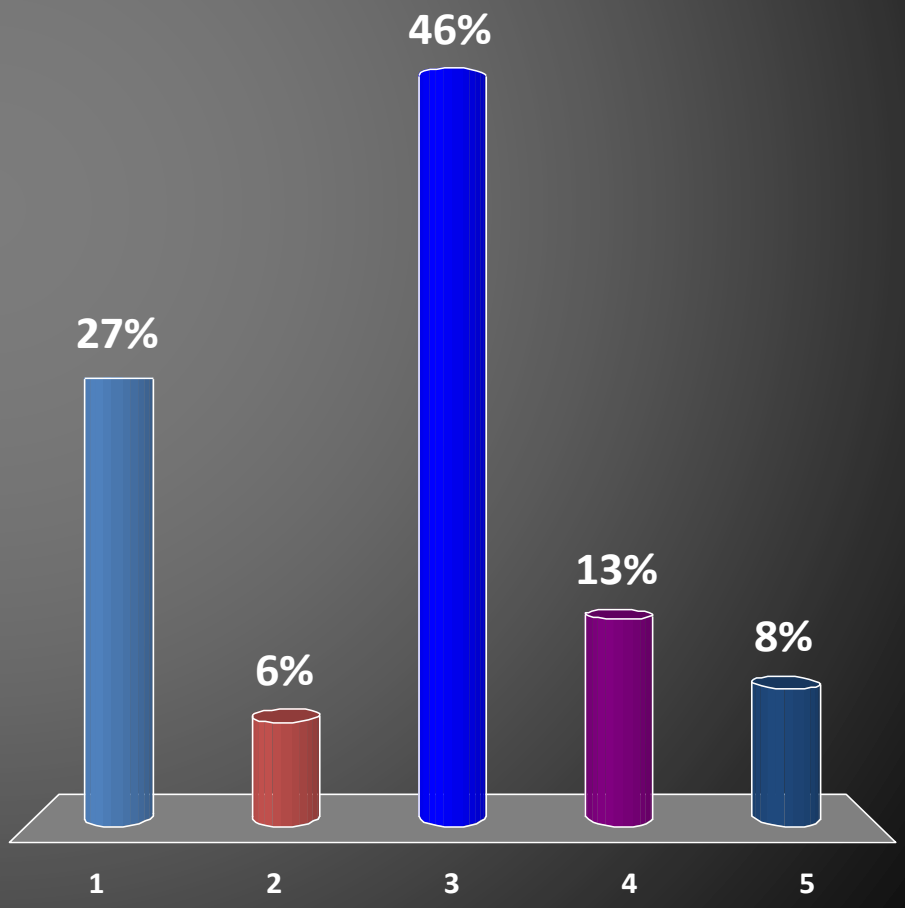


Owens RC, Ambrose PG. Clin Infect Dis. 2005;41:S144-S157

Question 2

Which of the following types of interaction between Biktarvy and dofetilide is the most likely mechanism contributing to proarrhythmia in this case:

1. Synergistic effects on I_{Kr}
2. Decreased glomerular filtration
3. Decreased dofetilide metabolism
4. Decreased intracellular potassium
5. Decreased active renal transport



Drugs with Proarrhythmic Potential (QT interval – page 1)

CredibleMeds Filtered QTDrug List

CREDIBLEMEDS™ powered by AZCERT.ORG

The last revision date: September 22, 2013

Filters: International Drugs - Drugs in US and some other nations; none

Generic Name	Brand Names	Drug Class	Therapeutic Use	TdP Risk Category	Route
Albuterol (salbutamol)	Proventil®, Ventolin®, Ventolin-HFA®, Accuneb®, Combivent®, Vospire-ER®, ProAir HFA®, Duoneb®	Bronchodilator	Asthma	Drugs to be avoided by congenital Long QT	oral,injection
Alfuzosin	Uroxatral®	Alpha1-blocker	Benign prostatic hyperplasia	Drugs with possible TdP risk	oral
Amantadine	Symmetrel®, Symadine®	Anti-viral	Anti-infective/ Parkinson's Disease	Drugs with conditional TdP risk	oral
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk	oral,injection

From www.crediblemeds.org

Relevant Pharmacology

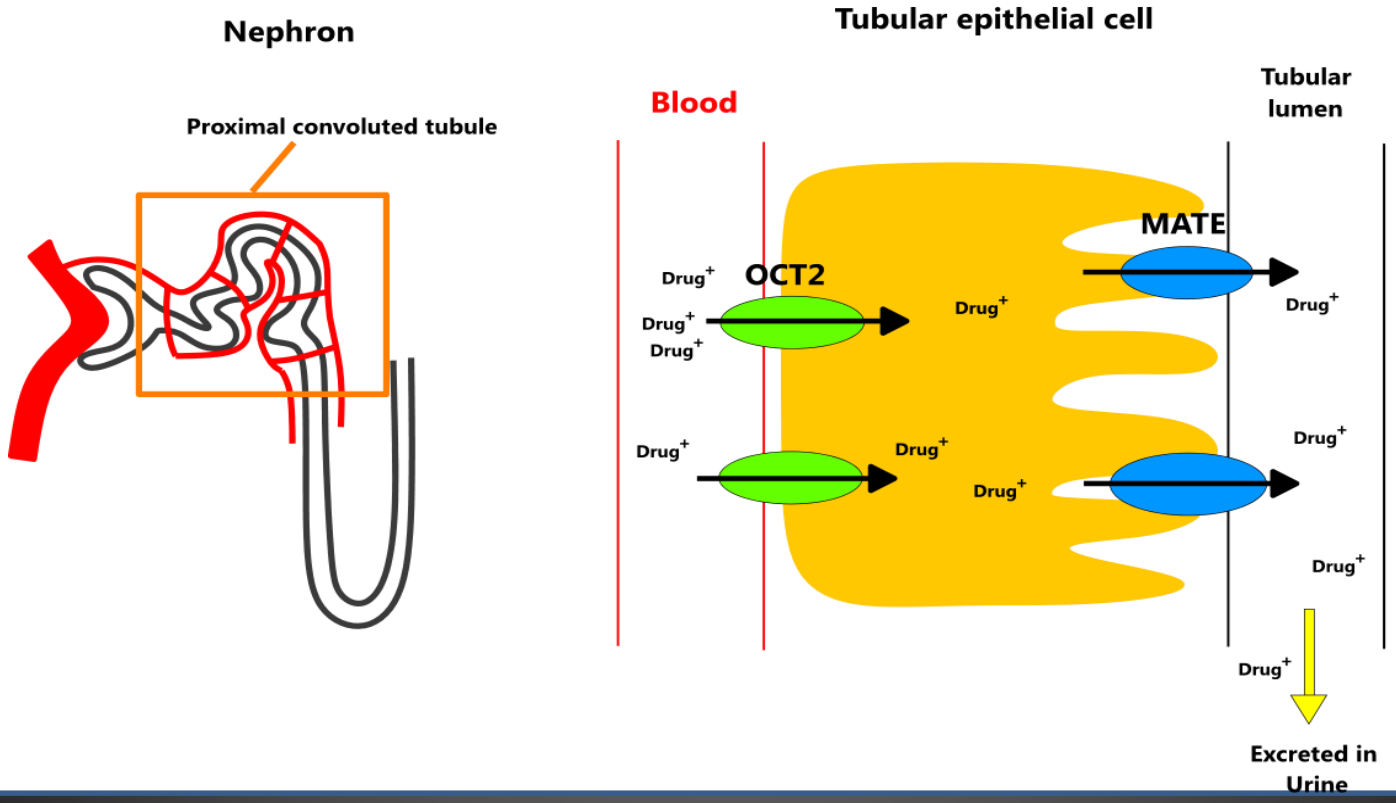
Dofetilide	
Bioavailability	>90%
Elimination Half-life	~10 hours
Elimination	80% renal 20% hepatic metabolism
Mechanism for renal clearance	Glomerular filtration Active tubular secretion (OCT2)

Ibuprofen	
Mechanism(s)	COX1 and COX2 inhibitor
	Reduced prostaglandin associated vasodilation and renal blood flow
	Acute and chronic interstitial nephritis

Organic Cation Transporter 2

Organic Cation Transporter 2 (OCT2)

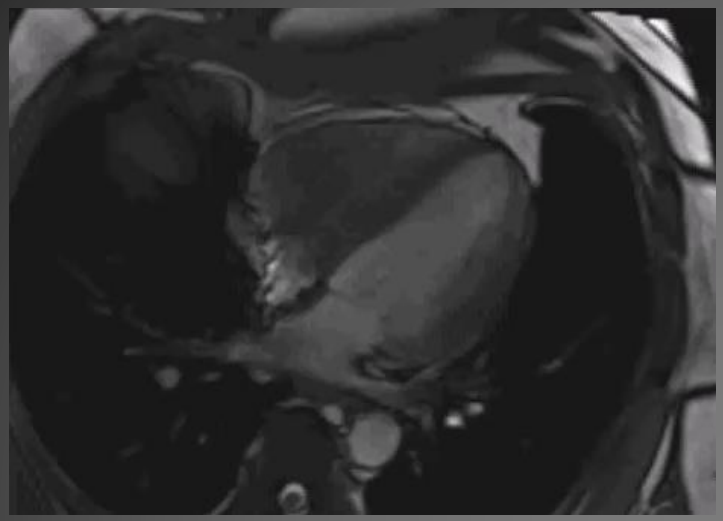
- OCT2 (SLC22A2) is a transport protein found in the kidney. It is located in the membrane of tubular epithelial cells in the proximal convoluted tubule.
- OCT2 transports drugs that have a positive charge (cations) from the blood supplying the proximal tubule to the inside of the tubular epithelial cell
- Multidrug And Toxin Extrusion proteins (MATE) then transport the cationic drug from inside the cell into the tubular lumen for excretion in the urine
- Some drugs inhibit OCT2 and/or MATE. Drug interactions may occur when OCT2/MATE inhibitors are taken with OCT2/MATE substrates.

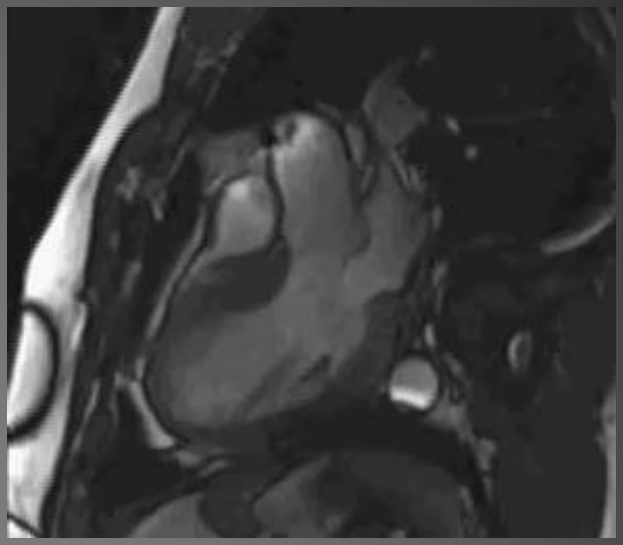


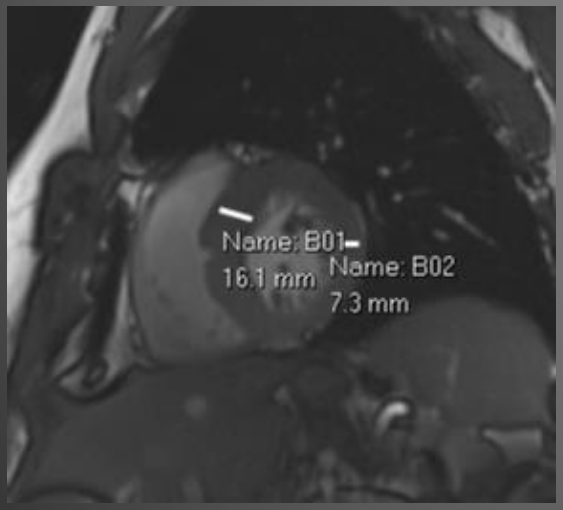
www.straighthealthcare.com/organic-cation-transporter-2.html

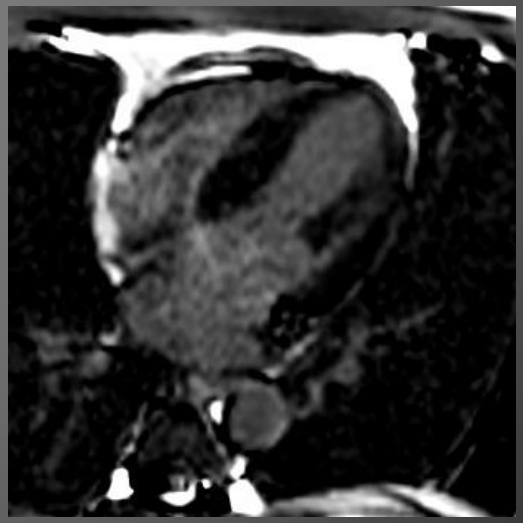
Case 2

A 49 year old man with no prior cardiac history presented 1 year ago with chest pain. He developed a NSTEMI with a peak troponin of 3.8. He received a DES for a tight left circumflex lesion. A follow-up 2DE showed an overall LVEF of 55% with mild inferior hypokinesis. The IVS measured 1.6 cm. A CMR study showed an IVS of 1.6 cm with asymmetric basal hypertrophy without obstruction and without LGE. He was discharged on aspirin, ticagrelor, atorvastatin and carvedilol.



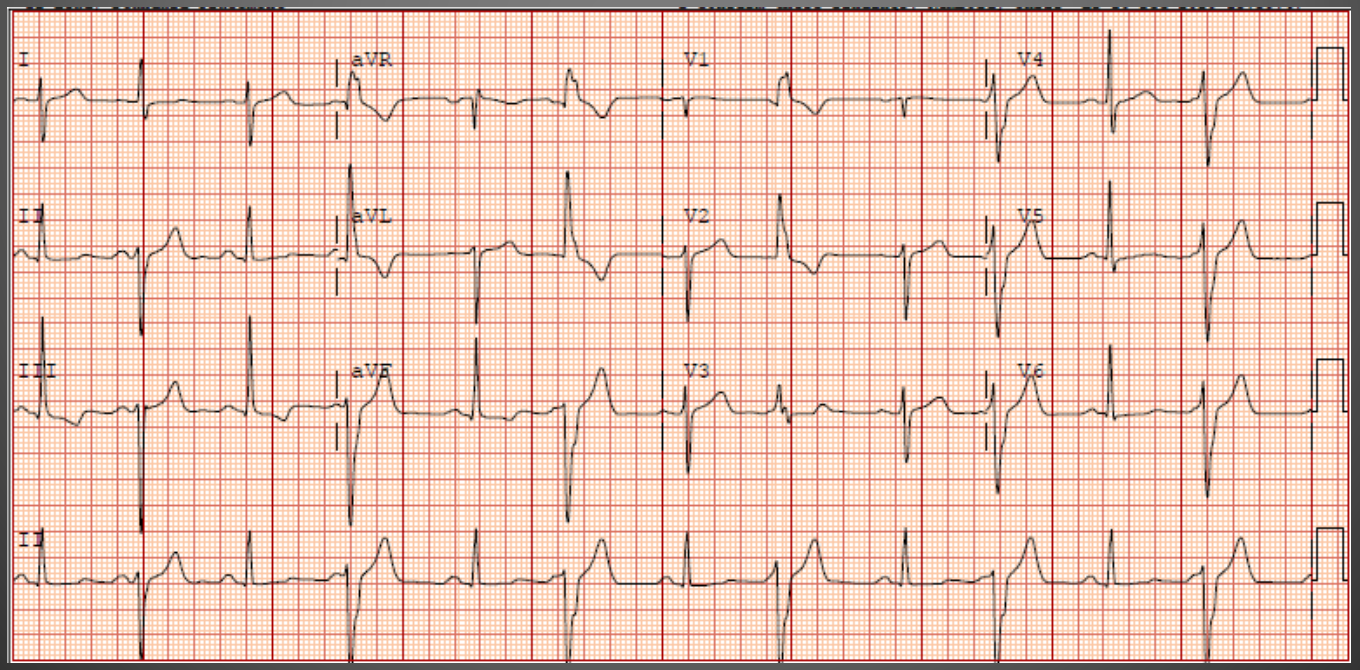



Name: B01
16.1 mm
Name: B02
7.3 mm



Case 2 continued

One month later he began to develop palpitations and dizziness. An ECG obtained at cardiac rehab is shown.



Case 2 continued

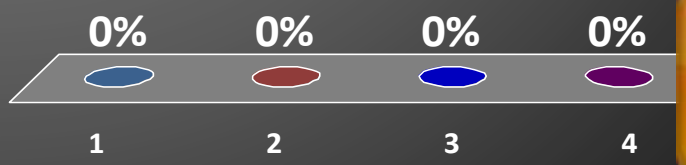
A 24 hour Holter monitor was obtained. The minimum and maximum HRs were 42 and 86 bpm; the average HR was 52 bpm. Ventricular counts are shown below. Dizziness correlated with bigeminy.

Ventricular Ectopy	6418
Sustained VT	
Nonsustained VT	
Ventricular Triplet	
Ventricular Couplet	
Ventricular Bigeminy	695
Ventricular Trigeminy	

Case 2 continued

What would you recommend now?

1. Increase carvedilol
2. Start amiodarone
3. Start sotalol
4. Schedule catheter ablation
5. No additional action



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Countdown

Case 2 continued

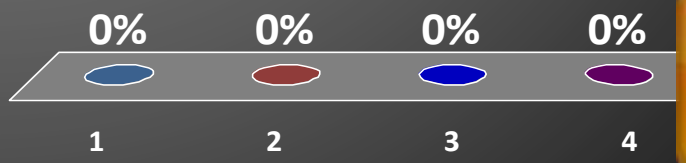
He was hospitalized for in-patient monitoring and started on sotalol reaching a dose of 120 mg bid. Carvedilol had been discontinued. His ventricular ectopy improved and the dizzy spells resolved.

Two weeks after discharge he collapsed at work. He was promptly resuscitated with an AED shock.

Case 2 continued

Sotalol is stopped. What would you do now?

1. Start amiodarone
2. Insert a S-ICD
3. Insert a single chamber ICD
4. Insert a dual chamber ICD
5. No further action.



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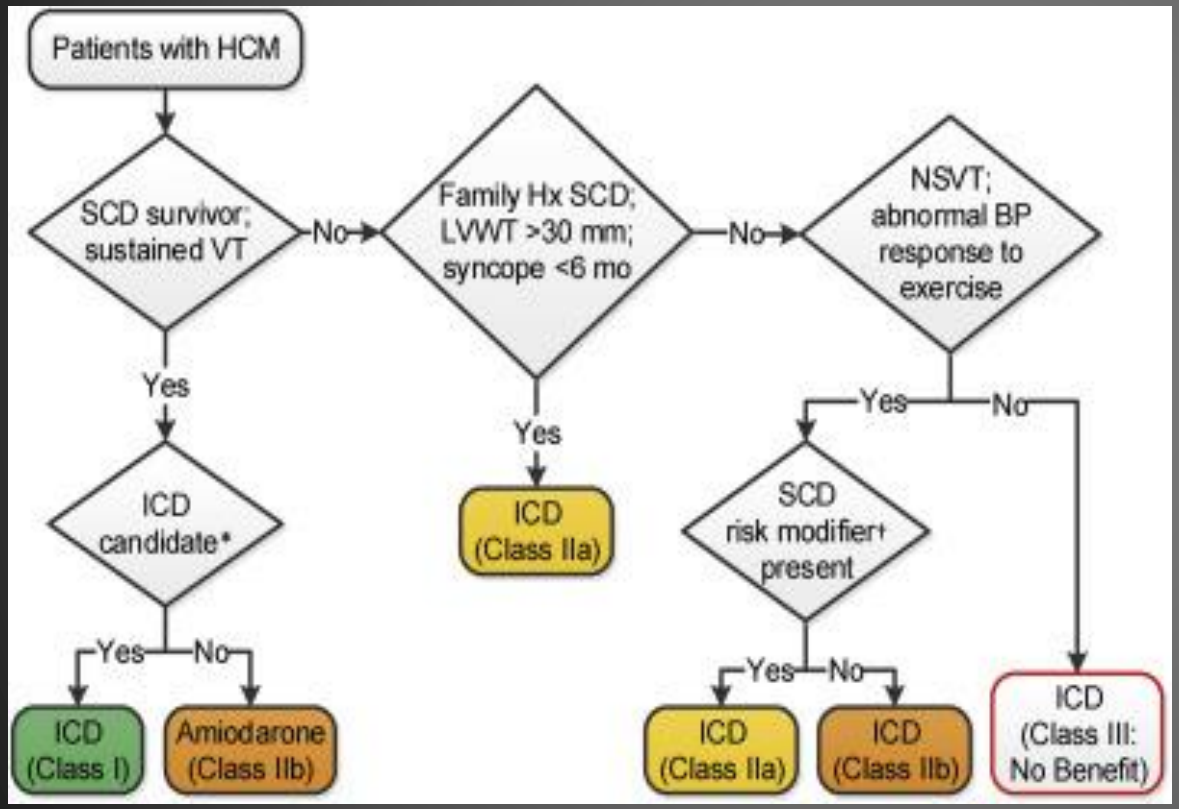
Countdown

2017 ACC/AHA/HRS



Established Risk Factors

1. Family hx of SCD associated w/ HCM
2. LV wall thickness >30mm
3. Unexplained syncope within 6 months
4. NSVT >3 beats
5. Abnormal BP response during exercise

Potential risk modifiers

1. < 30yo
2. LGE on CMR
3. LVOT obstruction
4. Syncope > 5 yrs ago

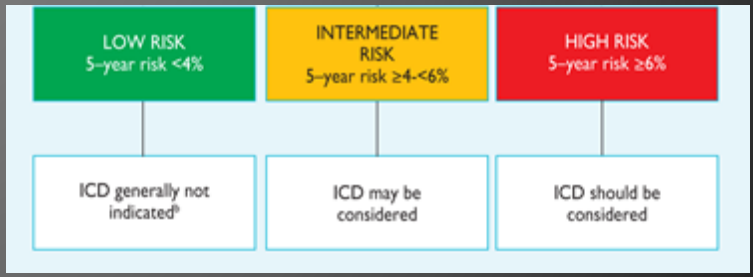
High Risk Subsets

1. LV aneurysm
2. LVEF <50%

ESC Risk Model – HCM Risk-SCD Score

- Mathematically derived quantitative risk score
- Developed due to thought that other risk algorithms fail to account for different effect size of individual risk factors
- Developed in accordance with O'Mahoney et al (2014, European Heart Journal)
  - Retrospective longitudinal cohort study of 3675 patients from 6 centers across Europe, median follow-up of 5.7 years
  - 198 patients (5%) had SCD or appropriate ICD shock
  - 7 Predictors associated with SCD/ICD shock
- 2014 ESC guidelines: Stratifies into 3 risk subsets based on predicted 5 year event rates
  - Low risk (<4%): ICD generally not recommended
  - Intermediate risk (4-6%): ICD may be considered
  - High risk >6%: ICD should be considered

Age	**Years**	*Age at evaluation*
Maximum LV wall thickness	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	**mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	○ No ○ Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ○ Yes	*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	○ No ○ Yes	*History of unexplained syncope at or prior to evaluation.*



Our patient prior to arrest if not on sotalol: 1.65%

Prevention of Proarrhythmia
The Future

- Predisposing genetic factors that influence ion channel activity and drug pharmacodynamics and pharmacokinetics will be fully characterized before an antiarrhythmic drug is started.

- Potential proarrhythmic drug interactions will flagged by pharmacy surveillance programs in a clinically relevant fashion.

- “Smart” ECG monitoring will detect early warning signs for proarrhythmia.