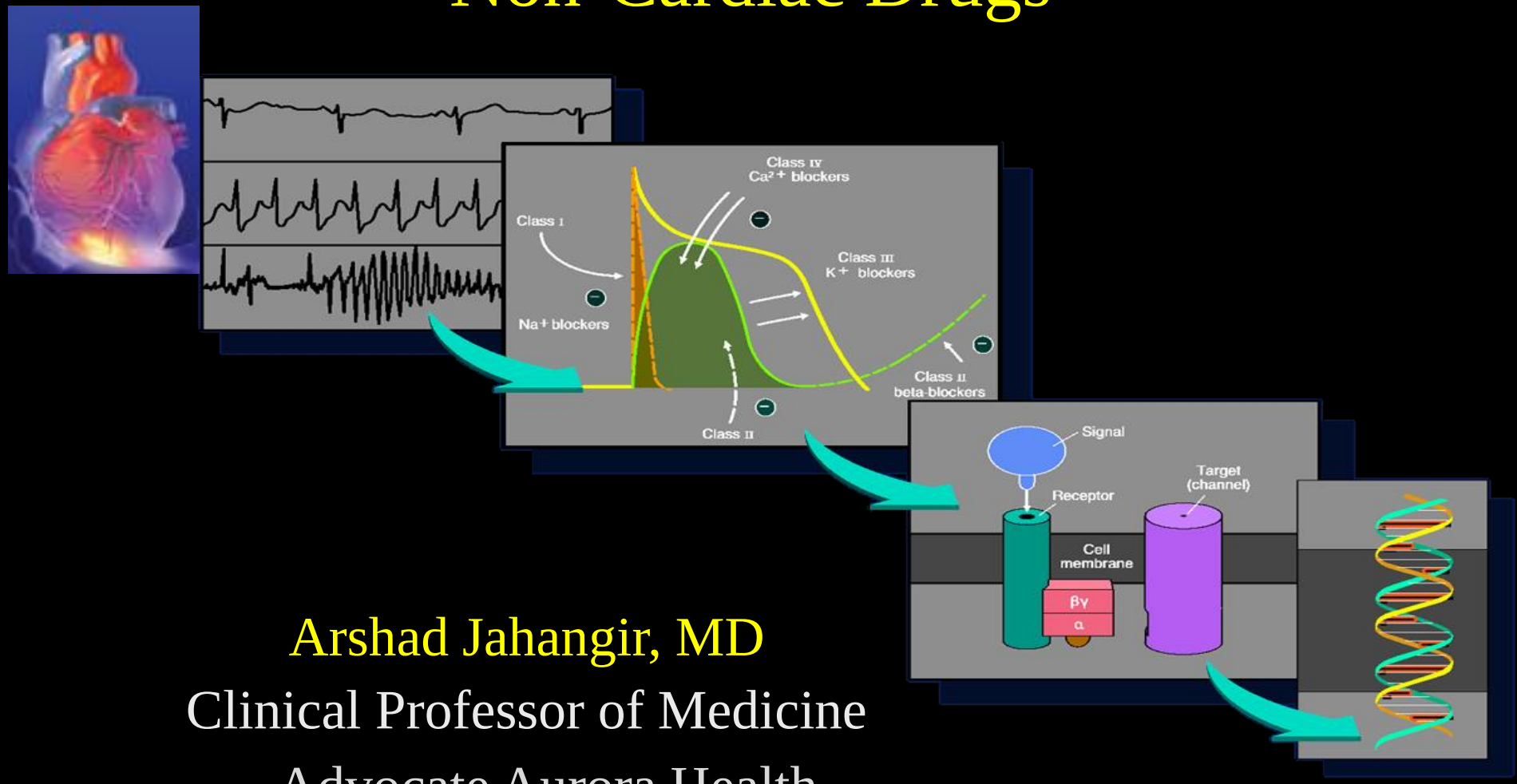
Proarrhythmic Effects of Non-Cardiac Drugs



Arshad Jahangir, MD

Clinical Professor of Medicine

Advocate Aurora Health
Milwaukee, WI

DISCLOSURE

Relevant Financial Relationship(s)

None

Case: 21 y/o Female with a History of Recurrent Syncope

- History consistent with vasovagal etiology
- F/Hx: -ve for syncope, SCD or arrhythmias
- Medical evaluation unremarkable
- Normal ECG
- Tilt table testing: vasodepressor response
- Treatment: conservative, fluids, salt

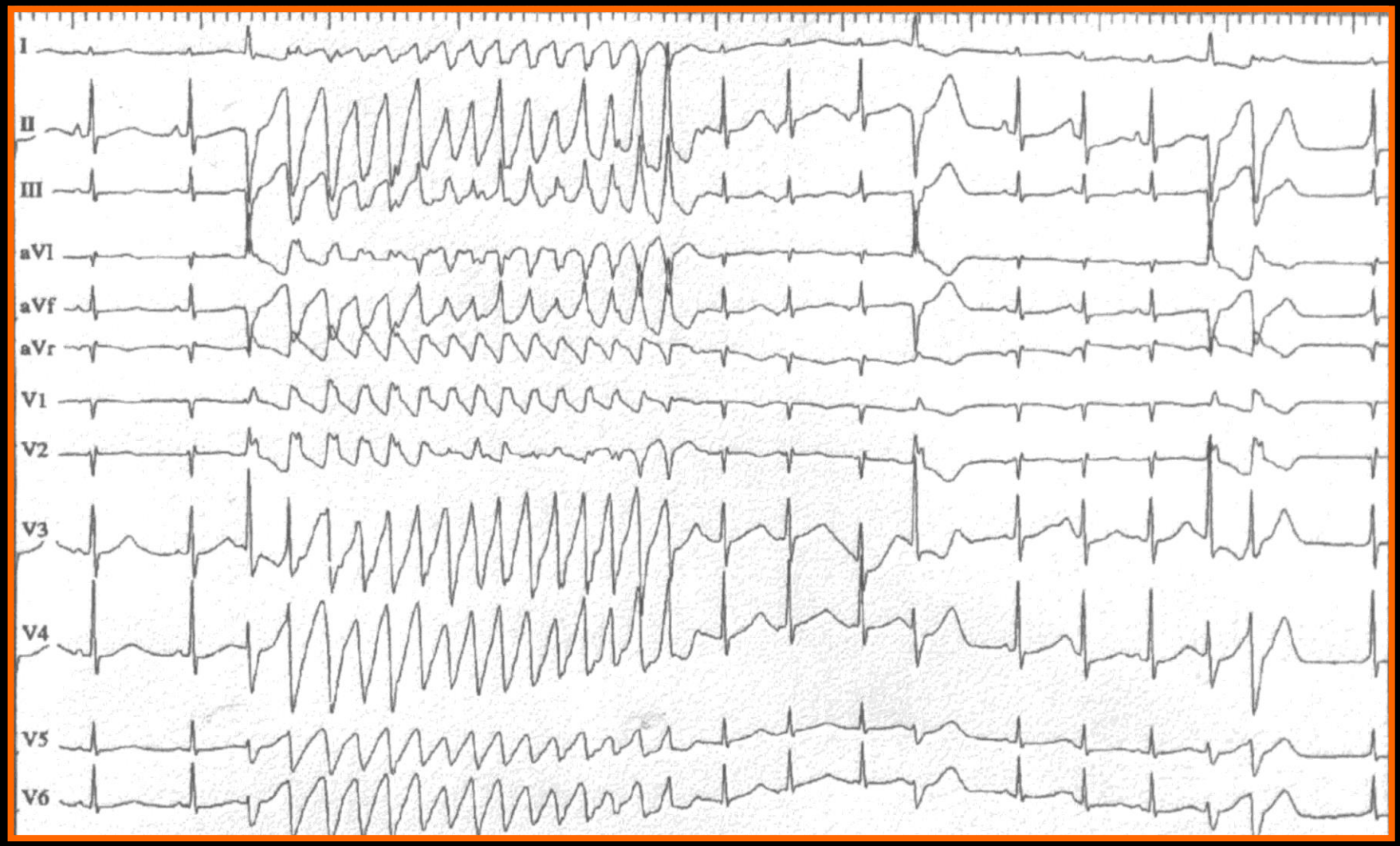
21 y/o Female with History of Syncope

ER visit,

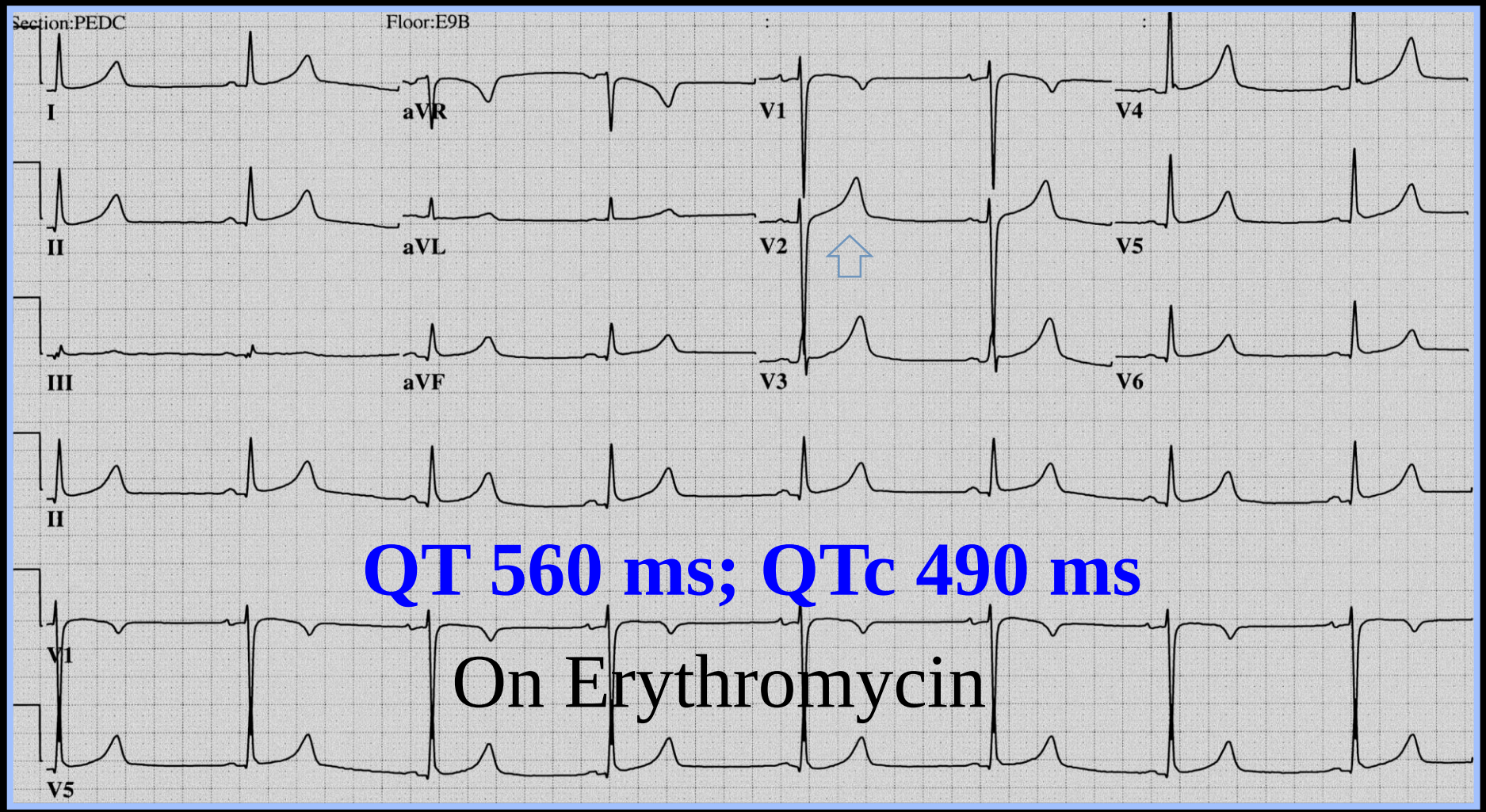
Two syncopal events

- **Both occurred at rest; preceded by a brief moment of palpitations**
- **Recent sinusitis; primary MD prescribed a medicine 3 days ago**

21 y/o with syncope



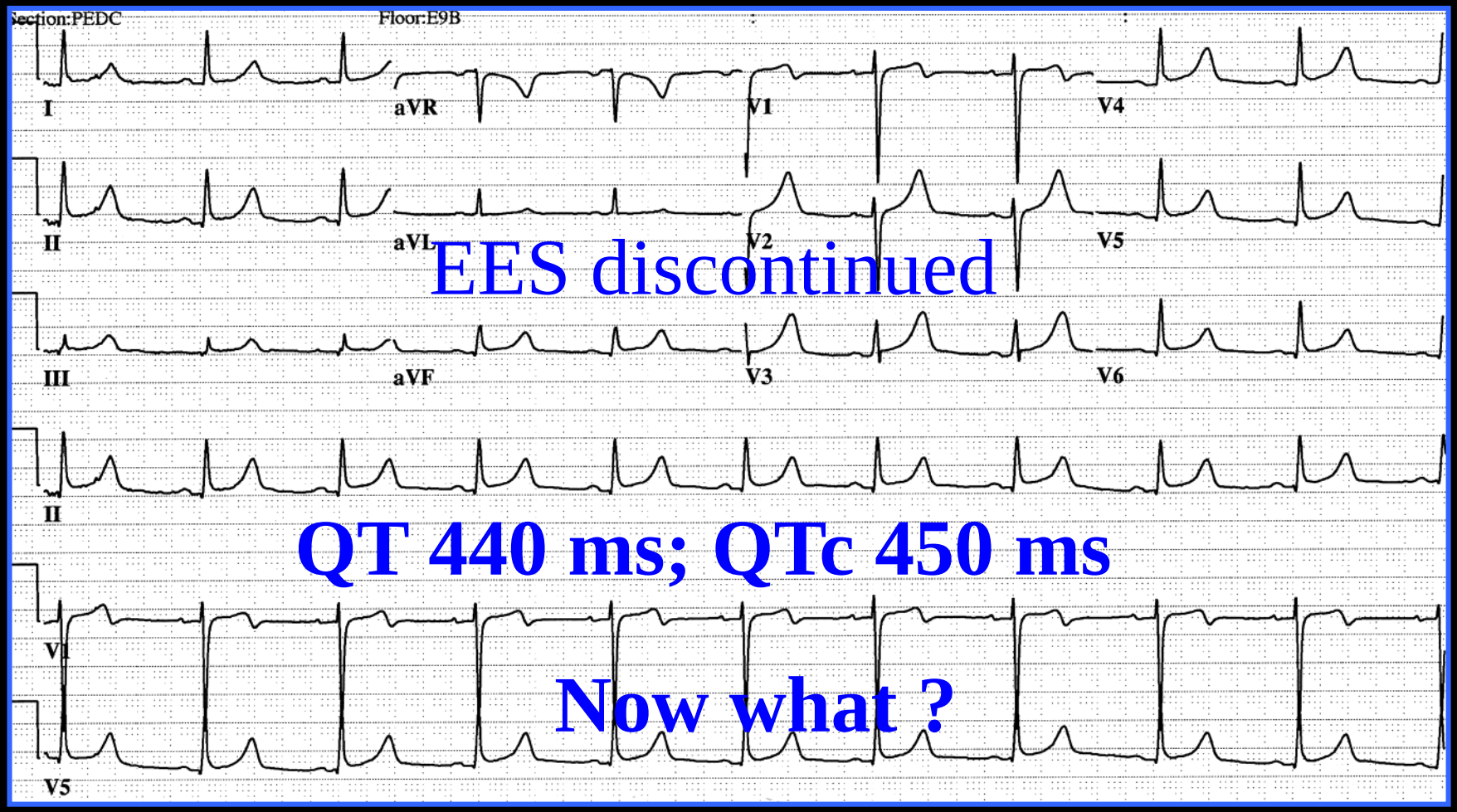
21 y/o with syncope



QT 560 ms; QTc 490 ms

On Erythromycin

21 y/o with palpitations and syncope

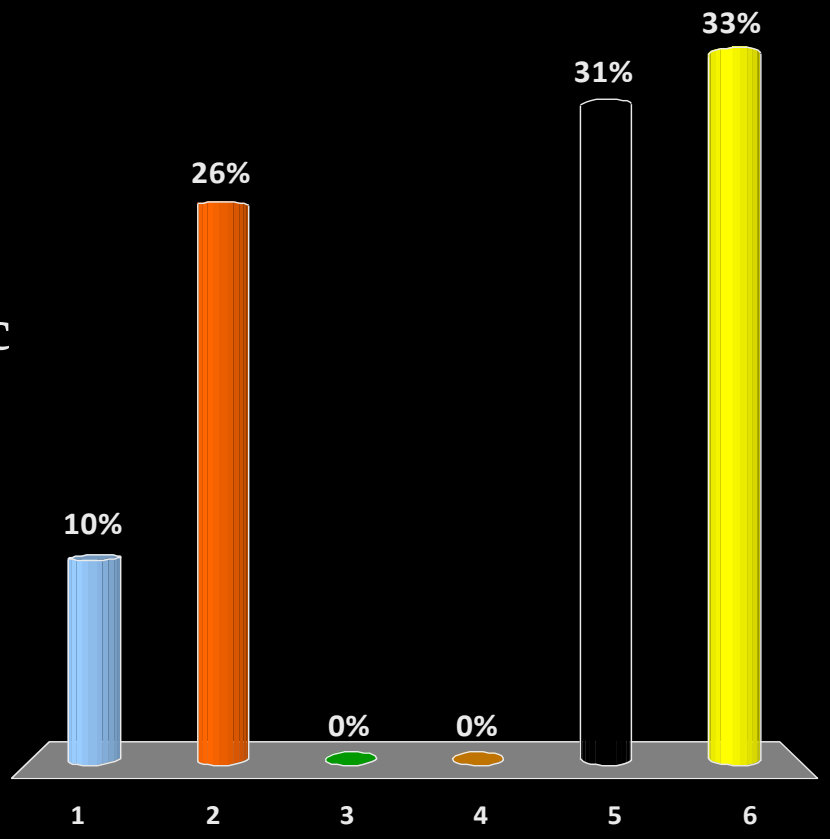


EES erythromycin ethylsuccinate

19-year-old female with history of syncope

What will you do next ?

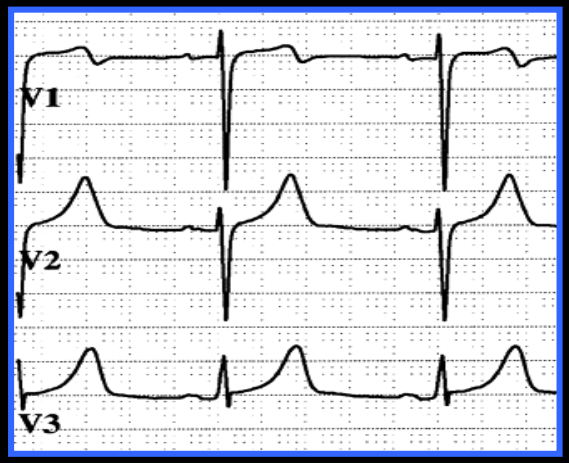
1. Start Levaquin, instead of Erythromycin
2. Start Beta-blocker therapy
3. Implant ICD
4. Consider left cardiac sympathetic neural denervation
5. No need for any intervention
6. None of the above



21-y/o Female with Syncope

- Is the episode primarily related to erythromycin effect on cardiac repolarization or she has a LQTS channelopathy
- Is she at high risk for cardiac arrhythmias and sudden cardiac death?
- Does she need an ICD for prevention of SCD?
- Are other family members at risk of cardiac arrhythmias?
- What advice should be given with regard to exercise, sports activity, pregnancy.

Case: Diagnosis and Therapy

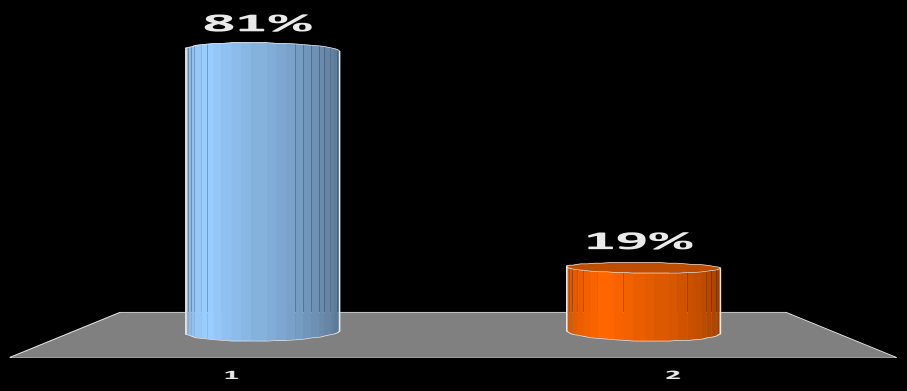


21-year-old female

- Erythromycin discontinued
- Beta blocker therapy started
- Avoidance of QT prolonging dugs (list)

Genetic testing for LQTS Genes ?

1. **Yes**
2. **No**



Prolonged QT Syndrome

Congenital / Familial

Autosomal Dominant

Romano-Ward Syndrome
(normal hearing), 1:2,000

Autosomal Recessive

Jervell and Lange-Nielsen Synd
(congenital deafness) Rare (1 in 10^6)

Sporadic

(normal hearing, nonfamilial ?)

17 genes:
KCNQ1 (IKs), KCNH2 (IKr), SCN5A (INa)

Acquired

Drugs
Electrolyte Abn
Bradyarrhythmias
Cardiomyopathy
Myocarditis
Cerebrovascular disease
Hypothyroidism

Concealed Long QT

Medications Related Pro-arrhythmia Risk
"Acquired" Channelopathy

- Cardiac and non-cardiac drugs (antibiotics, antidepressants, antipsychotics) can be proarrhythmic modulating ion channels (I_{Kr} I_{Na}) or PK/PD interactions with other drugs
- A major concern in drug safety
- A Modifiable risk factor for lethal arrhythmias and SCD

Molokha Br J Clin Pharm 2008 Cheng JACC 2015 Drew JACC 2010 Schwartz JACC 2016 Strauss EHJ

Medications Related Pro-arrhythmia Risk

"Acquired" Channelopathy

- The incidence of Drug-Induced SCD ?

  >15,000 deaths/yr ?

- TdP with sotalol, dofetlide 0.5-2%, quinidine 1.5-9%

  Initiated in-hospital with ECG monitoring

- Antibiotics, Antidepressants, antipsychotics

  Nortriptyline x 5-fold ↑ risk of SD (diLQT, diBrS)

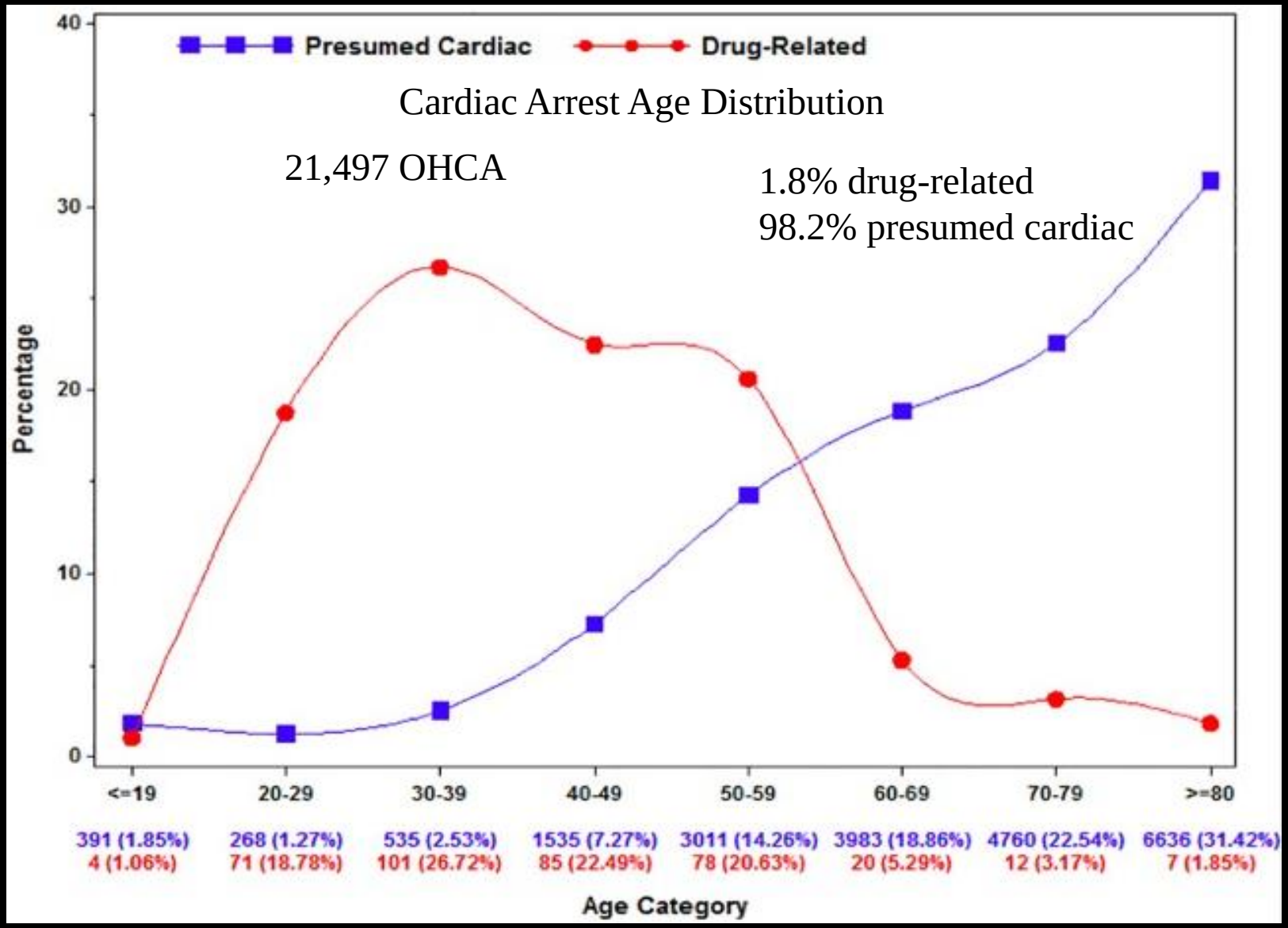
Recommendations for monitoring QT for QT-prolonging "noncardiac" medications in primary care settings, impractical.

1:8,500 serious arrhythmia on macrolides !

~ 1:30,000 can die

Molokha Br J Clin Pharm 2008 Cheng JACC 2015 Drew JACC 2010 Schwartz JACC 2016 Strauss EHJ

OHCA Drug-related *vs* Cardiac Causes
Ontario 2007-2013



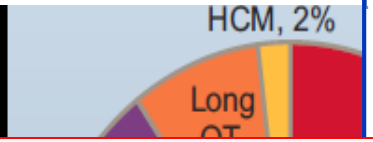
Orkin: PLoS ONE 2017;12:e0176441

The Washington Post
Democracy Dies in Darkness

Education

Student found dead in Catholic University dorm room

By **Peter Hermann**
November 7, 2018



U.S. & World

Student found dead on roof of college dorm

By: CNN

Posted: Dec 16, 2018 07:17 AM EST

Wisconsin Lutheran College student from Iowa found dead in her dorm room

Ray Hollnagel, Milwaukee Journal Sentinel Published 7:48 a.m. CT Jan. 21, 2019 | **Updated 3:31 p.m. CT Jan. 21, 2019**

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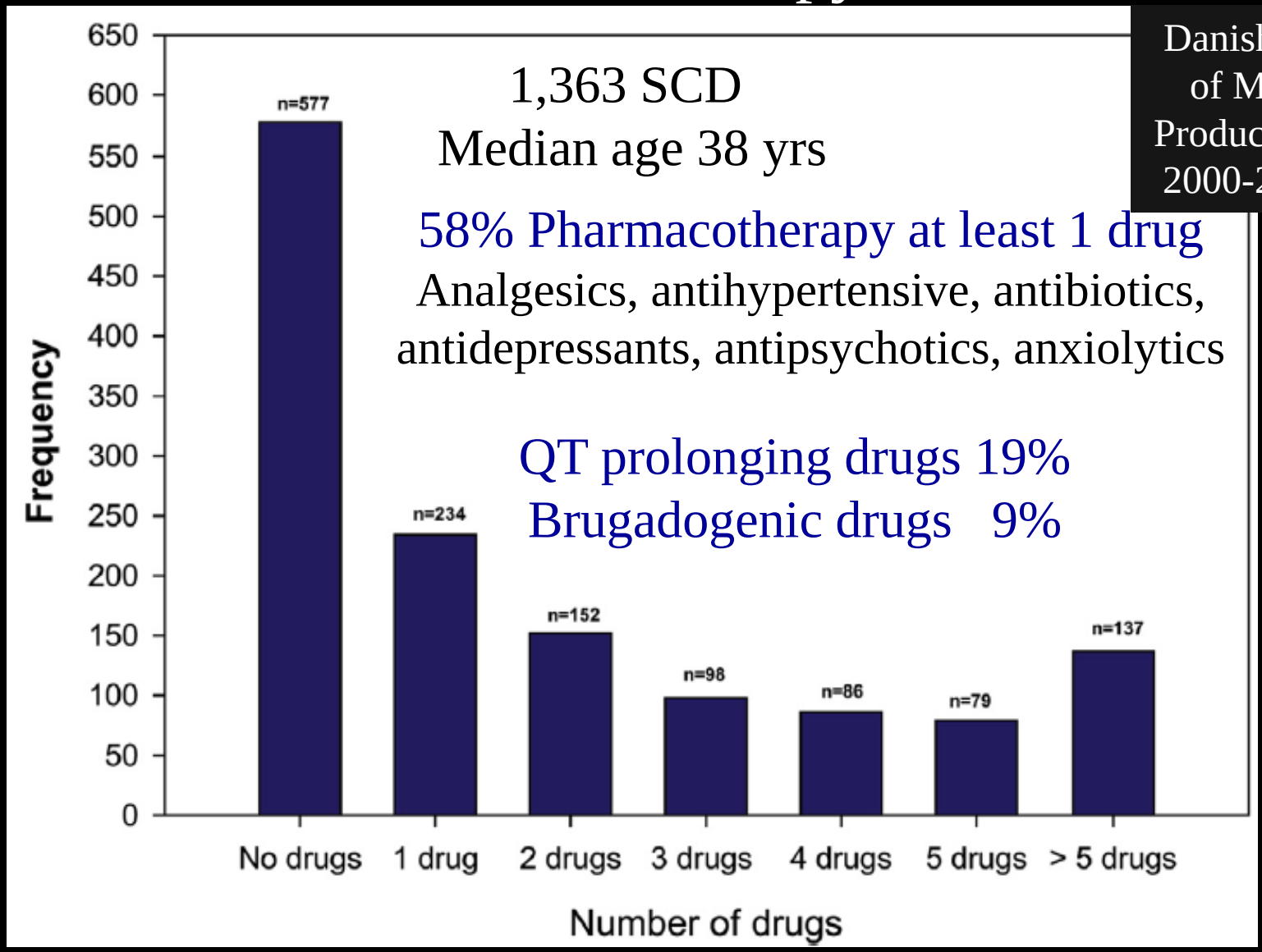
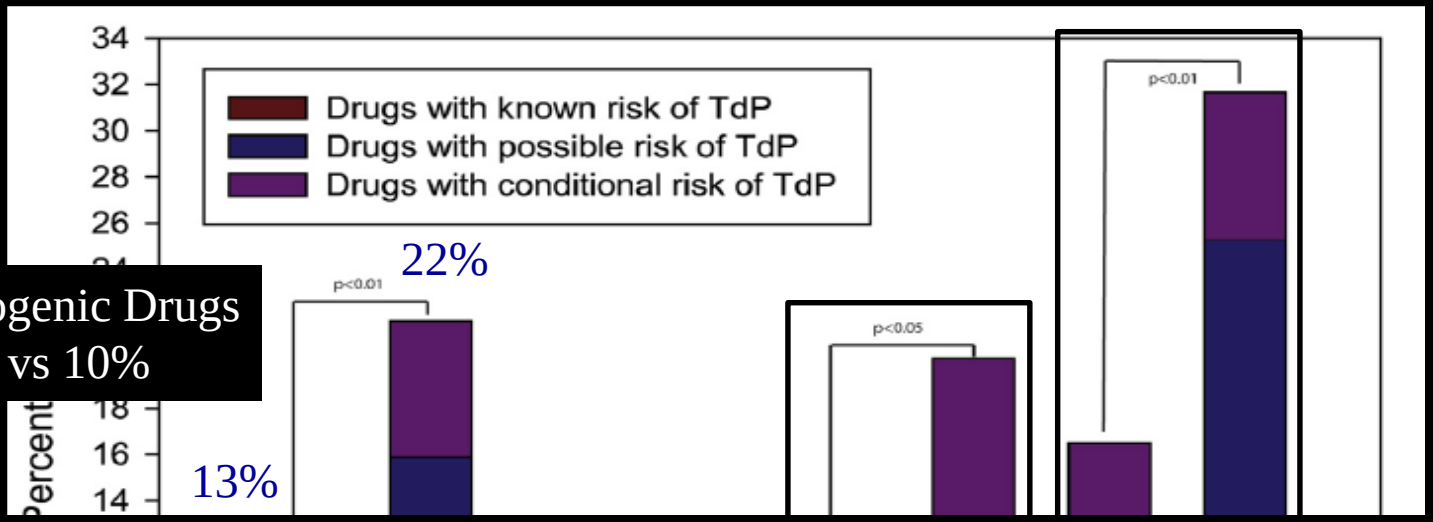
A Nationwide Cohort Study of Young Patients with SCD: Use of Pharmacotherapy Within 90 Days



Danish Registry of Medicinal Product Statistics 2000-2009 SCD

Risgaard: J Am Coll Cardiol EP 2017

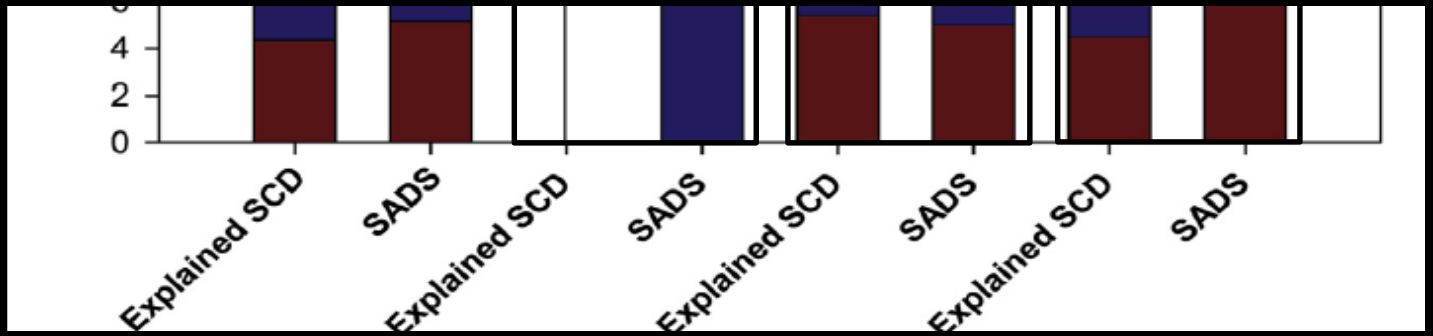
QT-Prolonging Drugs Prescription Within 90 Days of TdP /SCD in Young Patients



Brugadogenic Drugs
5% vs 10%

Drugs prescribed within 30 days before death, >1 QT↑ drug

SADS vs explained SCD OR: 3.48 (95%CI 1.85-6.52)



2- and 3-fold ↑ risk of SADS compared with explained SCD

Risgaard: J Am Coll Cardiol EP 2017 A Nationwide Cohort Study in Denmark

QT Prolonging Drugs

Antiarrhythmics

- IA: Quinidine, procainamide, disopyramide
- III: Sotalol, NAPA, ibutilde, dofetilide, amiodarone

Antimicrobials

antibiotics: Macrolides, TMP/SMX, Fluoroquinolones

antifungals: itraconazole, ketoconazole

antimalarials: chloroquine

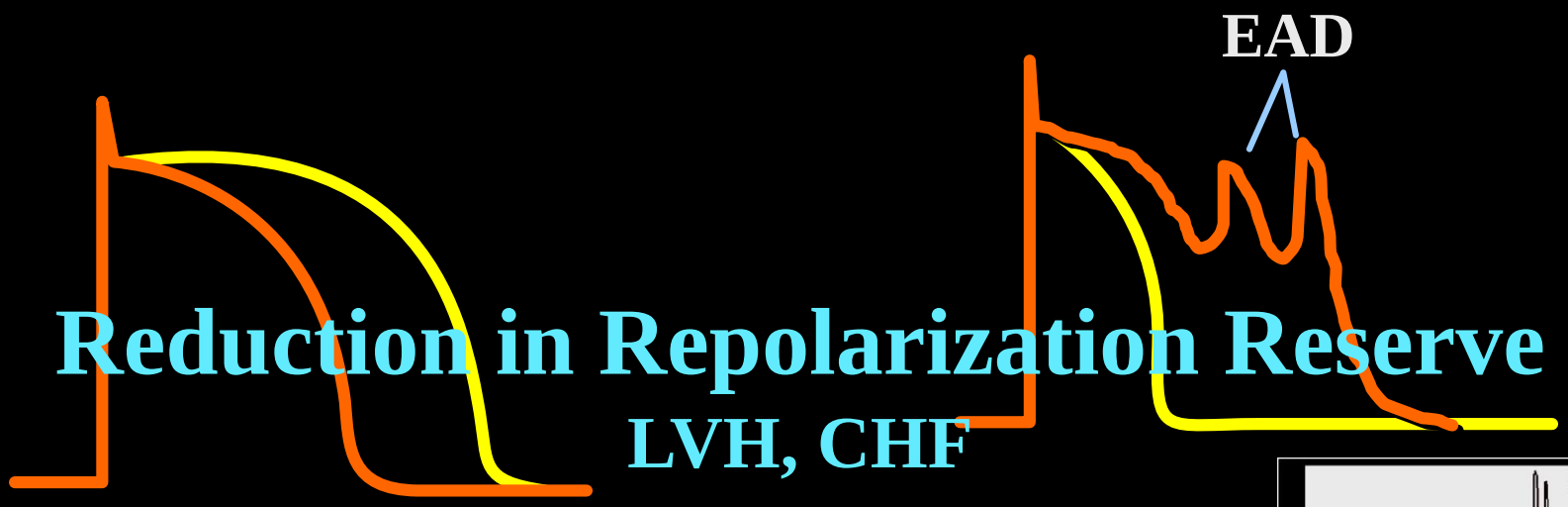
antiparasitic: pentamidine

antivirals: amantadine

- Antihistamine
  - (Terfenadine, asetmizole)
- Antidepressants
  - Tricyclics, tetracyclics, SSRI
- Psychotropics
  - Haloperidol, droperidol,
  - Phenothiazines
- Antiemetics
  - Ondansetron
- Antineoplastics
  - Arsenic trioxide, CsCl, Pt, TKI, HDACi, Anthracyclines, Trastuzumab
- Opiods
  - Methadone, loperamide*
- Miscellaneous
  - Metamphetamine
  - Metoclopramide
  - (Cisapride)
  - Organophosphate poisoning

crediblemeds.org

Proarrhythmia with K^+ Channel Bockers



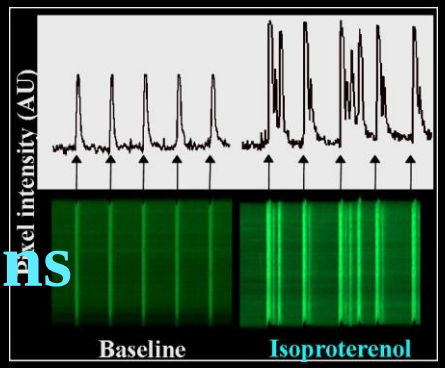
Reduction in Repolarization Reserve

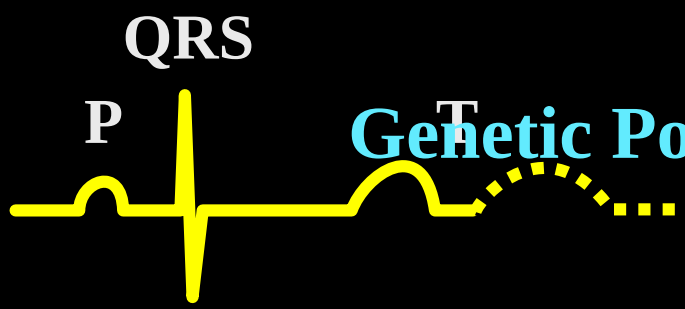
LVH, CHF

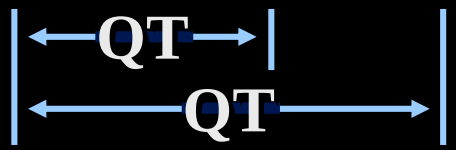
DM, Age, F

Medications

Genetic Polymorphism/ mutations



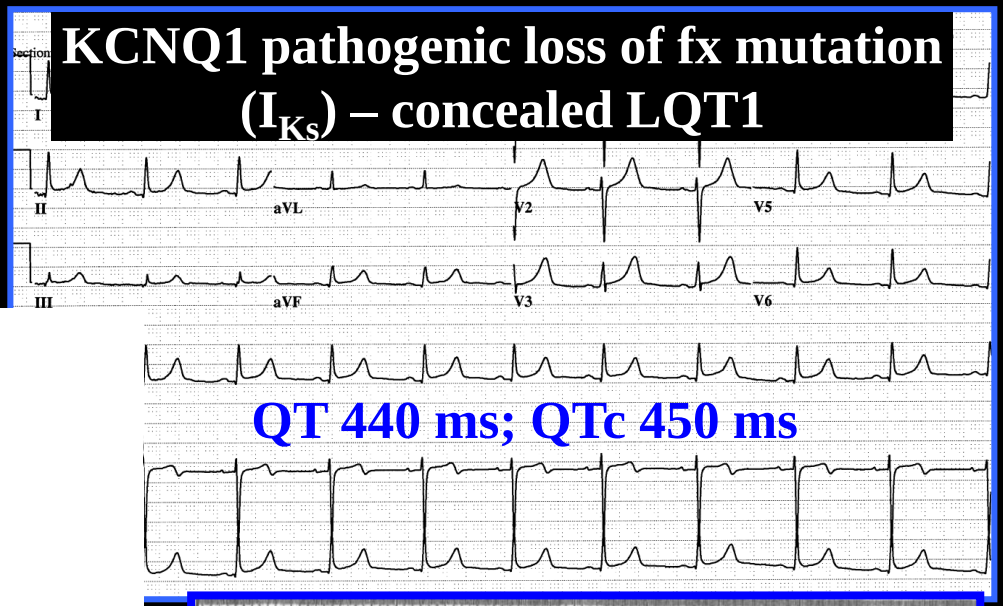




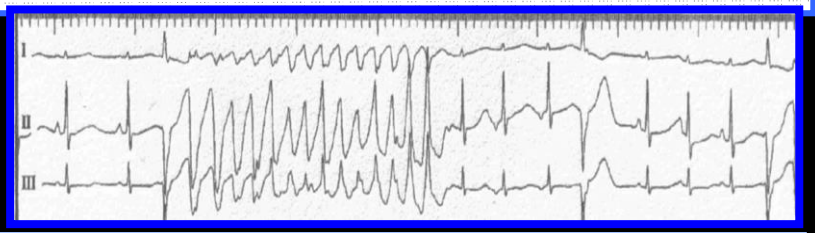
Torsade de pointes

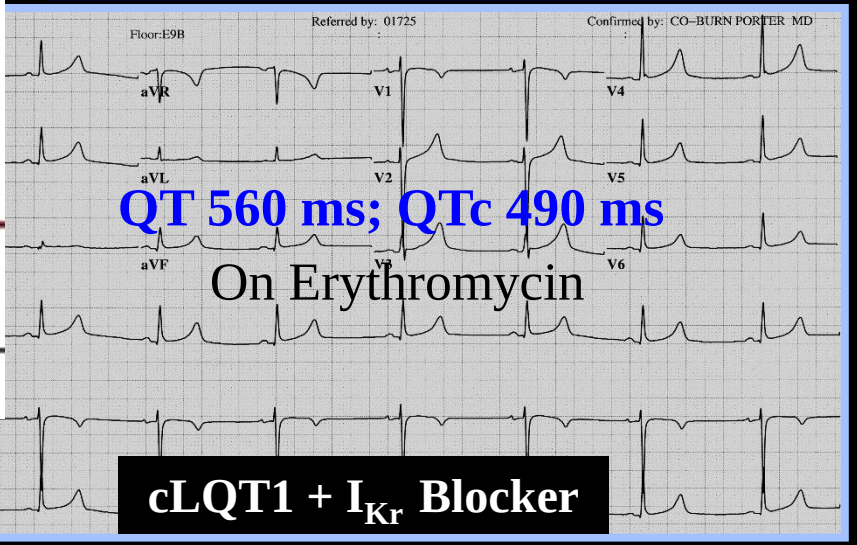
Sanguinetti: 1997

KCNQ1 pathogenic loss of fx mutation (I_{Ks}) – concealed LQT1



QT 440 ms; QTc 450 ms

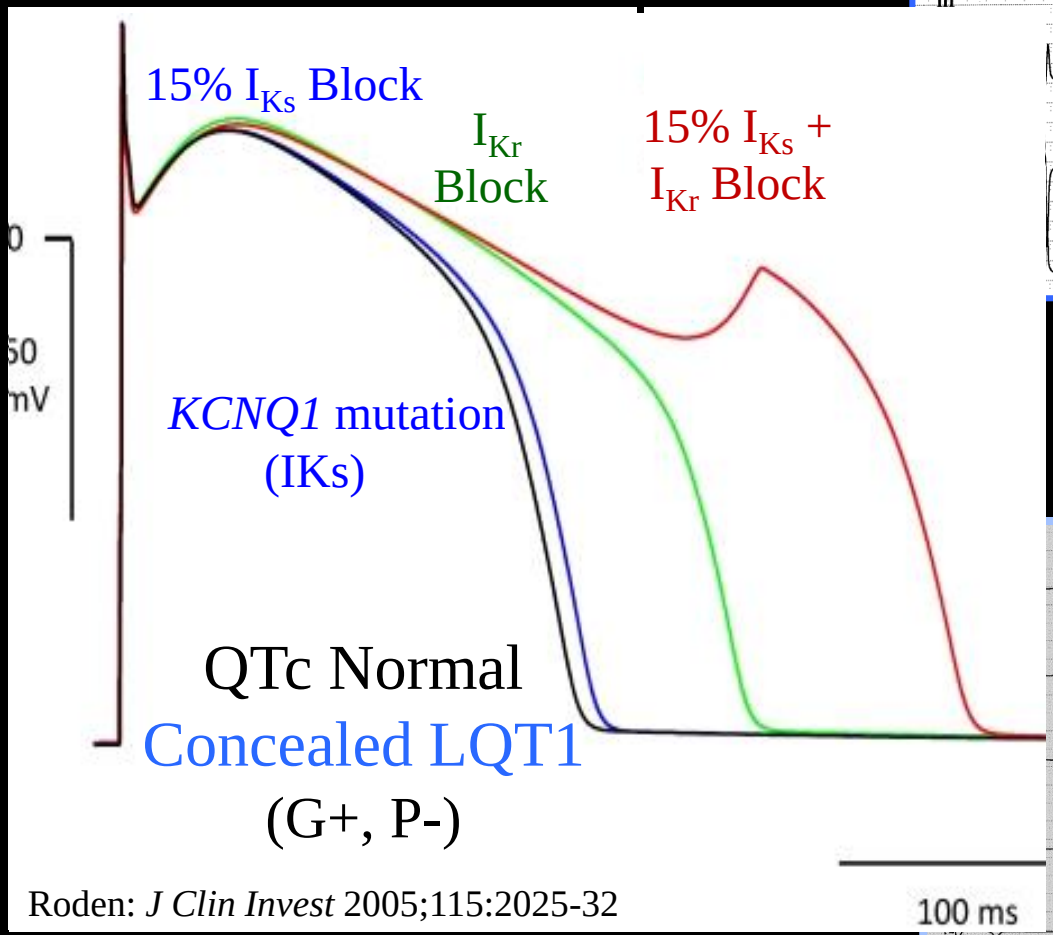




QT 560 ms; QTc 490 ms

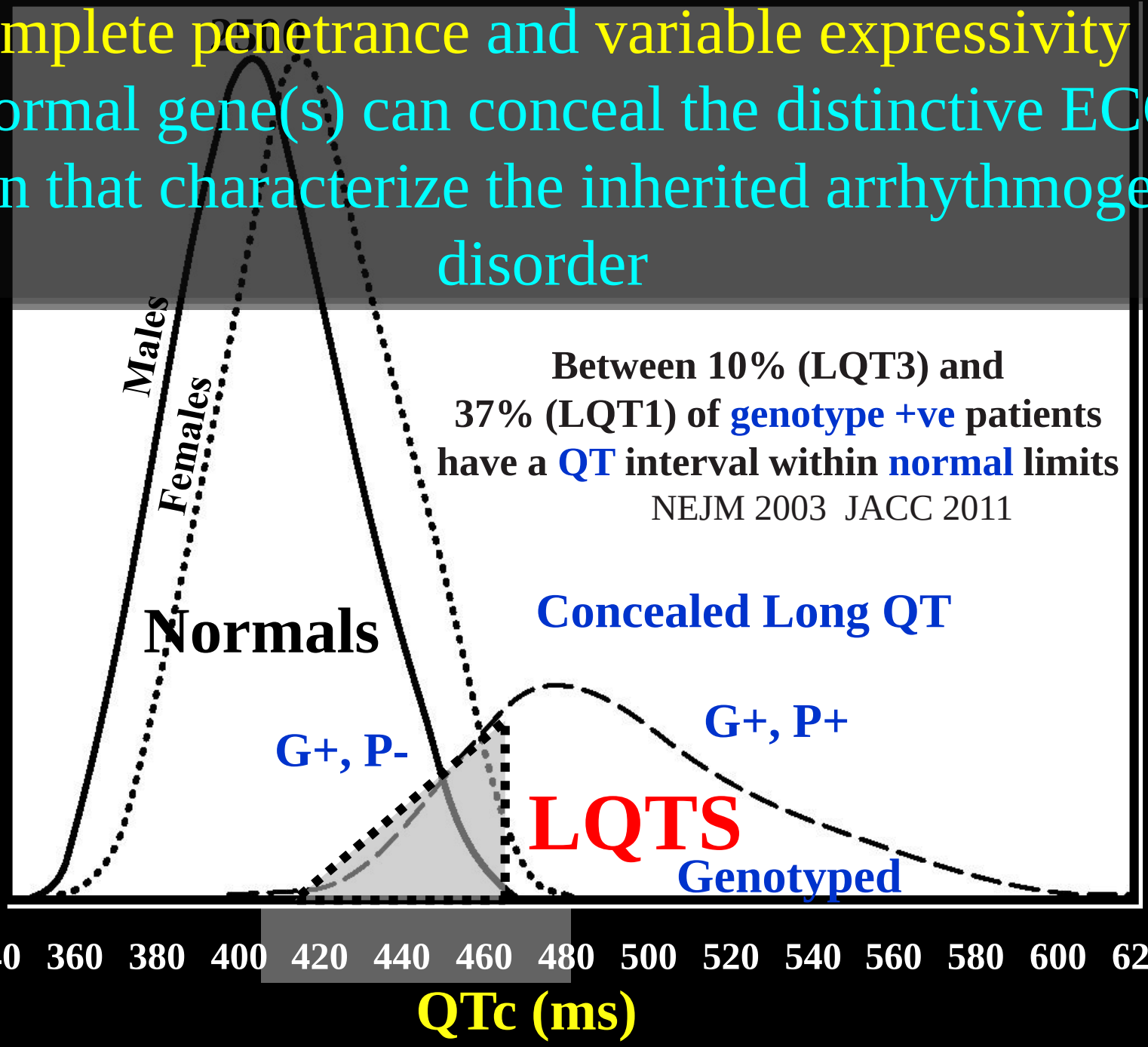
On Erythromycin

cLQT1 + I_{Kr} Blocker



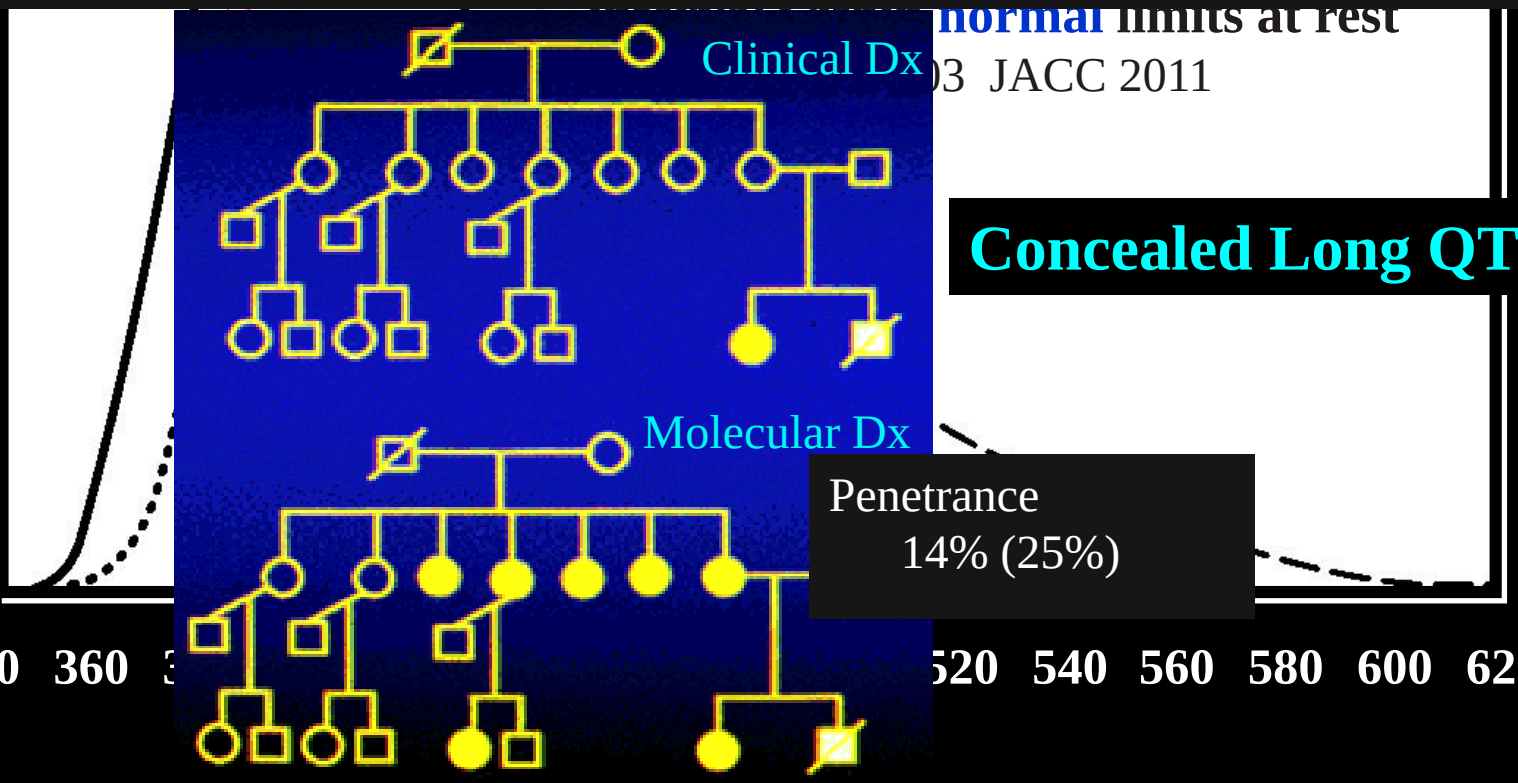
Roden: *J Clin Invest* 2005;115:2025-32

Incomplete penetrance and variable expressivity of abnormal gene(s) can conceal the distinctive ECG pattern that characterize the inherited arrhythmogenic disorder

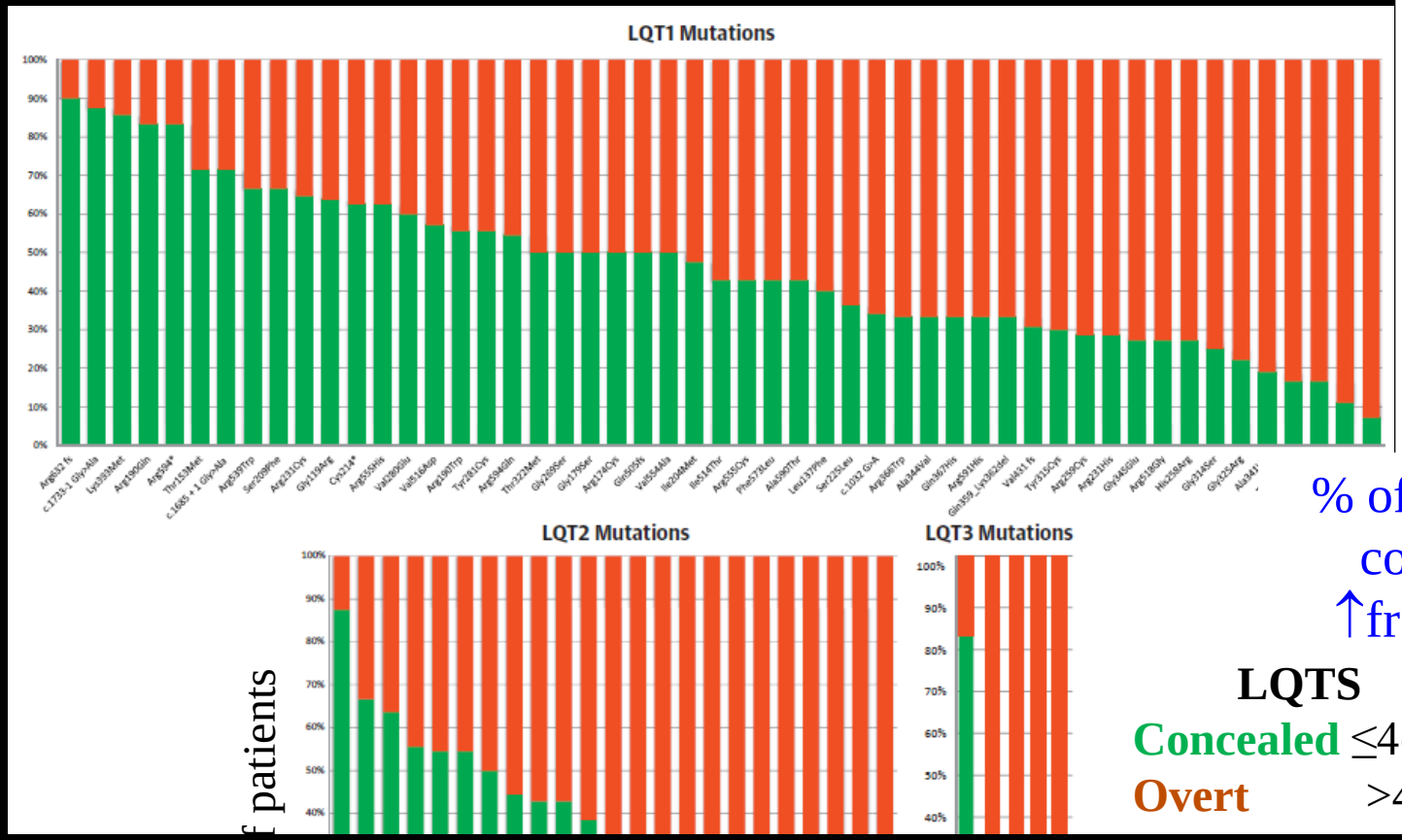


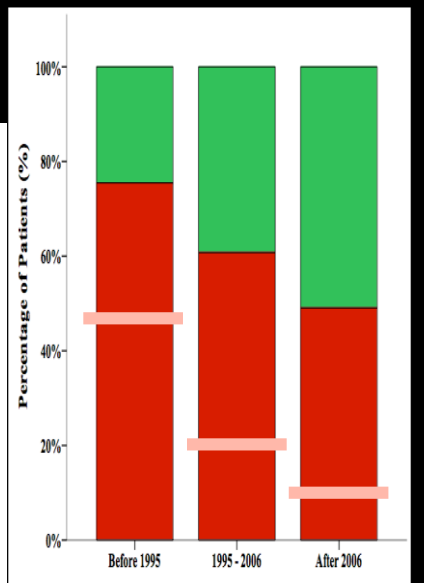
Incomplete penetrance and variable expressivity of abnormal gene(s) can conceal the distinctive ECG pattern that characterize the inherited arrhythmogenic disorder

- ~20% of drug-induced LQT cases shown to have LQTS-associated mutations *vs* 4% in control population



Penetrance of LQTS Phenotype According to Genotype





% of individuals with concealed LQTS ↑from 23% to 50%

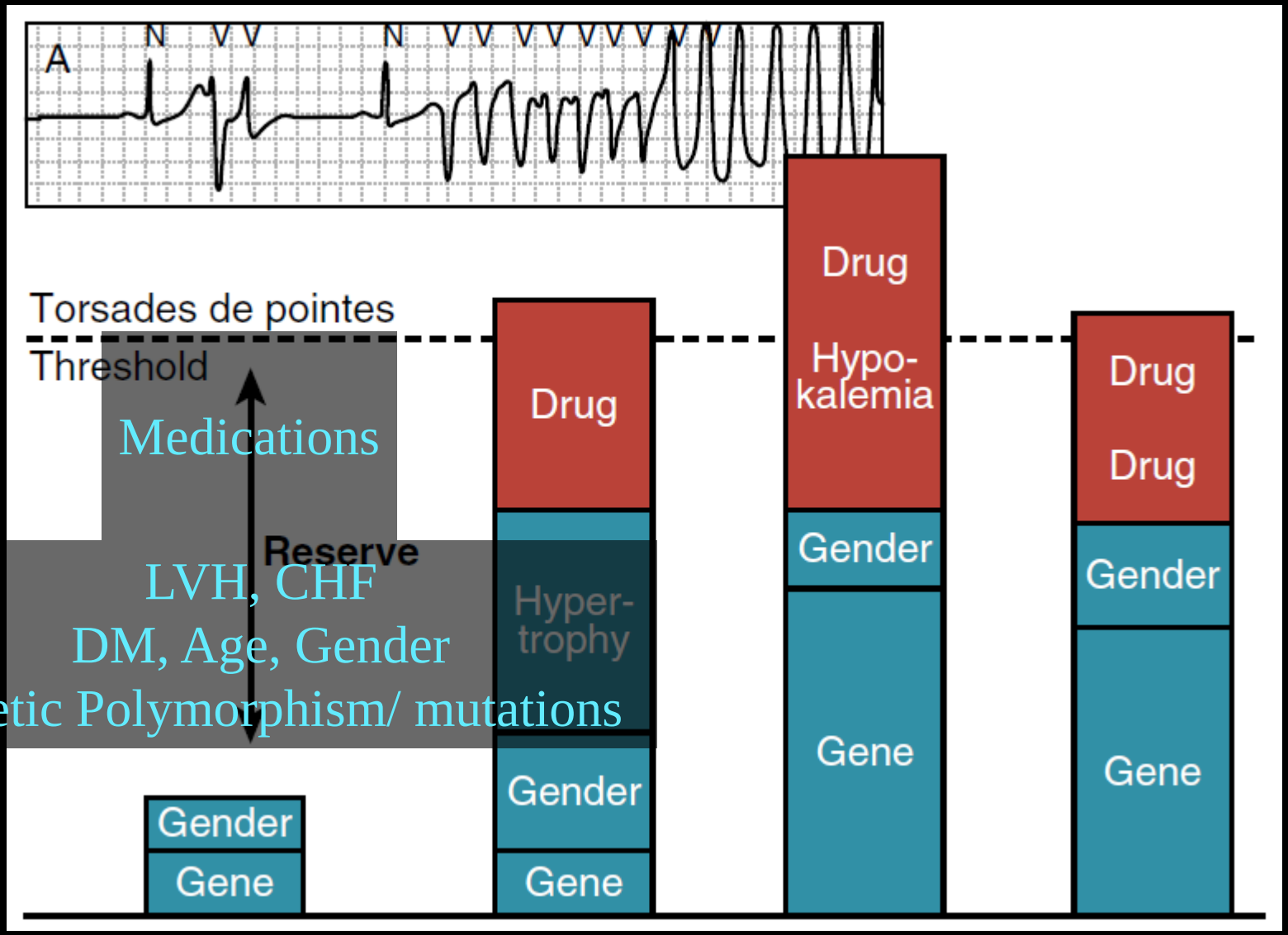
LQTS

Concealed ≤460 ms

Overt >460 ms

- Avoidance of unnecessary prescriptions of QT↑ drugs
- Awareness - physicians and patients
- Screening ???

The Concept of Repolarization Reserve

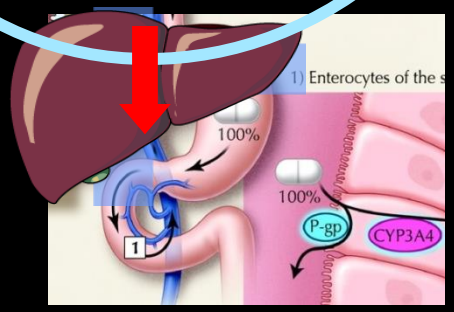


Eckardt & Breithardt

Important Pharmacokinetic Considerations

Genetic Variants
Drug interactions

Drug → CYP3A4



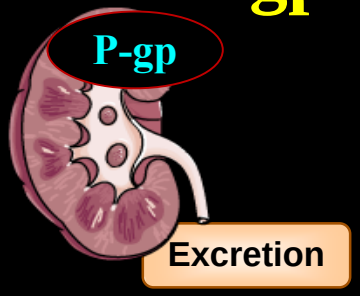
↑ Bioavailability (levels)

↑ Toxicity

Inhibitors CYP3A4
- Azole antifungals
- Erythromycin
- Cimetidine
- Diltiazem, Verapamil
- Protease Inhib (HIV
- Amiodarone, Dronedarone

Grapefruit Juice

P-gp



Inhibitors CYP2D6
Fluoxetine, SSRI

CYP3A4 QT ↑ → TdP

Dofetilide*, Quinidine, Amiodarone
Dronedarone, CaChBl
Erythromycin,
Rivoraxaban, Apixaban
TCA, Methadone

CYP2D6
Thioridazine, Methadone
Flecainide, Propafenone,
↑ NaCh-blockade

CYP2C9*3
Warfarin Bleeding

Drug-Induced QT Prolongation

Excessive QT Prolongation or Changes in T morphology

ΔQT_c 30 ms from baseline or QTc >470 ms

ΔQT_c 60 ms or QTc >500 ms

- Direct effect on repolarization (dose/duration)
- Drug-drug / drug-supplement Interactions
  - Pharmacodynamics
  - Pharmacokinetics
    - metabolic inhibition- metabolites
    - renal clearance
- Drug-substrate Interactions
  - Cardiomyopathy, LVH, low LVEF, SND
  - Liver/ renal disease
  - Underlying Gentic susceptibility
    - Polymorphisms/ mutations

Risk factors for TdP with drug-induced QT Prolongation

Demographic: Female sex, age

Electrolytes: ↓ K^+, Mg^{2+}

Genetic predisposition: Channelopathies, DNA polymorphism

Cardiac - Baseline QT, Concealed LQT, Bradycardia, pauses

- Recent cardioversion, AVJ ablation with sudden HR slowing
- cardiomyopathy (HF, LVH, MI)

Systemic Conditions - Hepatic impairment, Renal Impairment

Concomitant Drugs - >1 QT prolonging drugs, drugs inhibiting metabolism, diuretics, digoxin

Thank You

Identification of Young Patients at Risk for SCD

- Prodromal Symptoms/signs
  - Aborted CA, Exertional Syncope, VT-palpitations
- Screening Test - Monitoring
  - Cost and inconvenience of untargeted screening
  - Sens of test, Disease prevalence, Cost (test, false +ve), Rx
  - ECG, TMET, Echo - ECG Alerts
  - Targeted screening of family members (phenotype, cascade testing)
- Risk Stratification (known cardiac disease)
  - LQTS, HCM, BrS, CPVT, ARVC, LVDysfx
- Risk Factors for drug-induced adverse effects - Alerts
  - Patient-specific, Drug-specific (dofetilide, sotalol)
    Dynamic factors (repolarization reserve - drug-drug-disease interaction) - ECG Alerts

Back

IATROGENICITY

CAUSES AND CONSEQUENCES OF IATROGENESIS IN CARDIOVASCULAR MEDICINE

EDITED BY

IHOR GUSSAK

AND

JOHN KOSTIS

Co-Edited by

I. Akim • M. Borggrefe • G. Campanile • A. Jahangir • W.J. Kostis • G.X. Yan

RUTGERS UNIVERSITY PRESS MEDICINE

Minimizing Risk of drug-induced TdP

In Drug Development

- Preclinical screening: invitro and invivo – “thorough QT/QTc test”

Regulation and postmarketing surveillance

- Risk/benefit - RCT
- appropriate warnings, monitoring requirements
- Postmarketing surveillance
  - withdrawal (astemizole, terfenadine, cisapride, grepafloxacin, thioridazine)

Minimizing Risk of drug-induced TdP

In Drug Development

- Preclinical screening: invitro and invivo – “thorough QT/QTc test”

Regulation and postmarketing surveillance

- Risk/benefit - RCT
- appropriate warnings, monitoring requirements
- Postmarketing surveillance

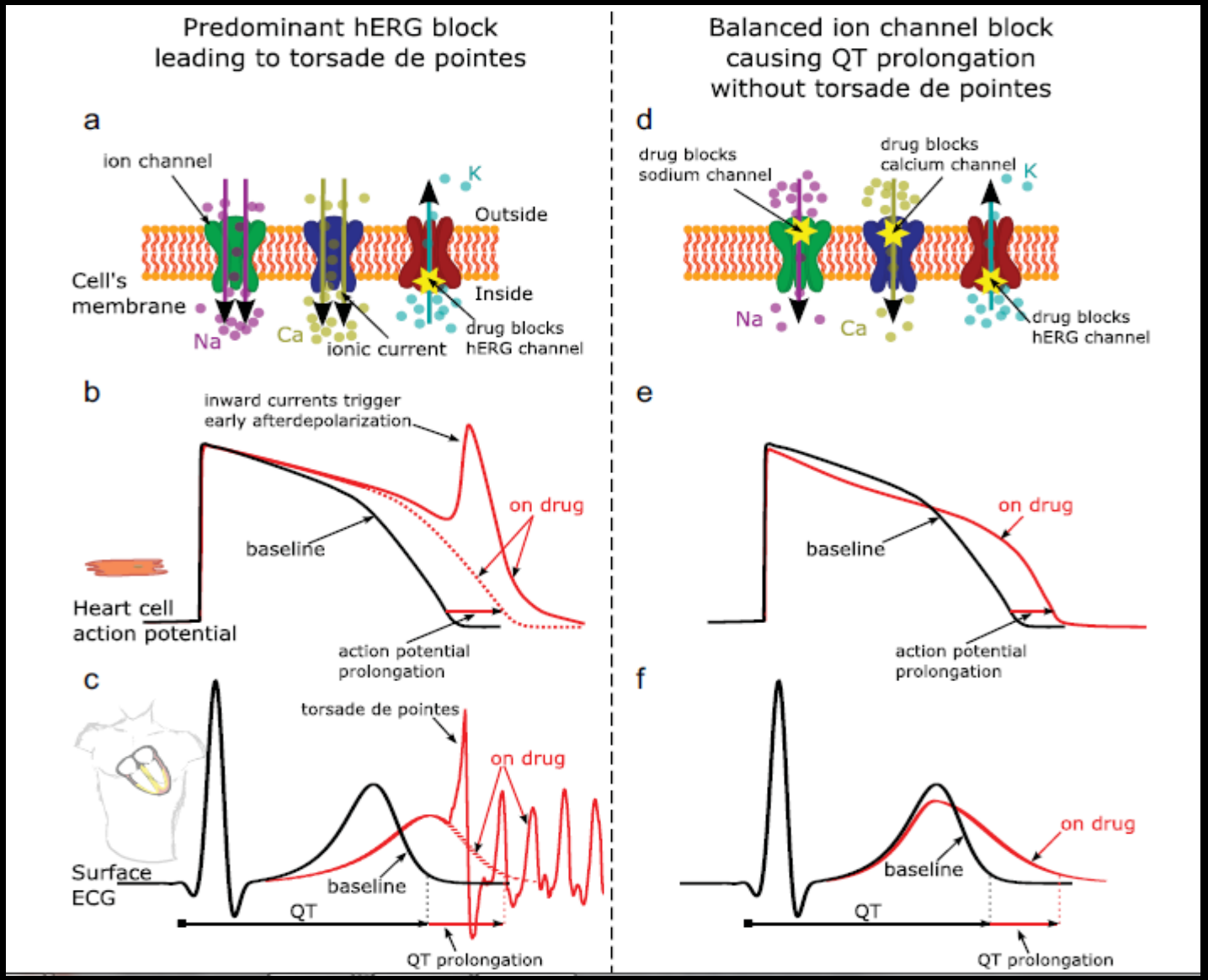
16 000 screening ECGs are needed to identify a single case of asymptomatic long QT syndrome (Rodday: Pediatrics 2012129-e999-1010

Minimizing Risks in Clinical Practice

- Recommendations are lacking
  - Avoidance of QT drugs (https://crediblemeds.org)
  - Patient Education (Sx, concomitant use of drugs)
  - Assessment of Risk factors – cardiac, systemic, external
  - Modifiable risk factors (drugs, electrolytes, OSA)
  - ECG screening ? - High risk
    monitoring ?

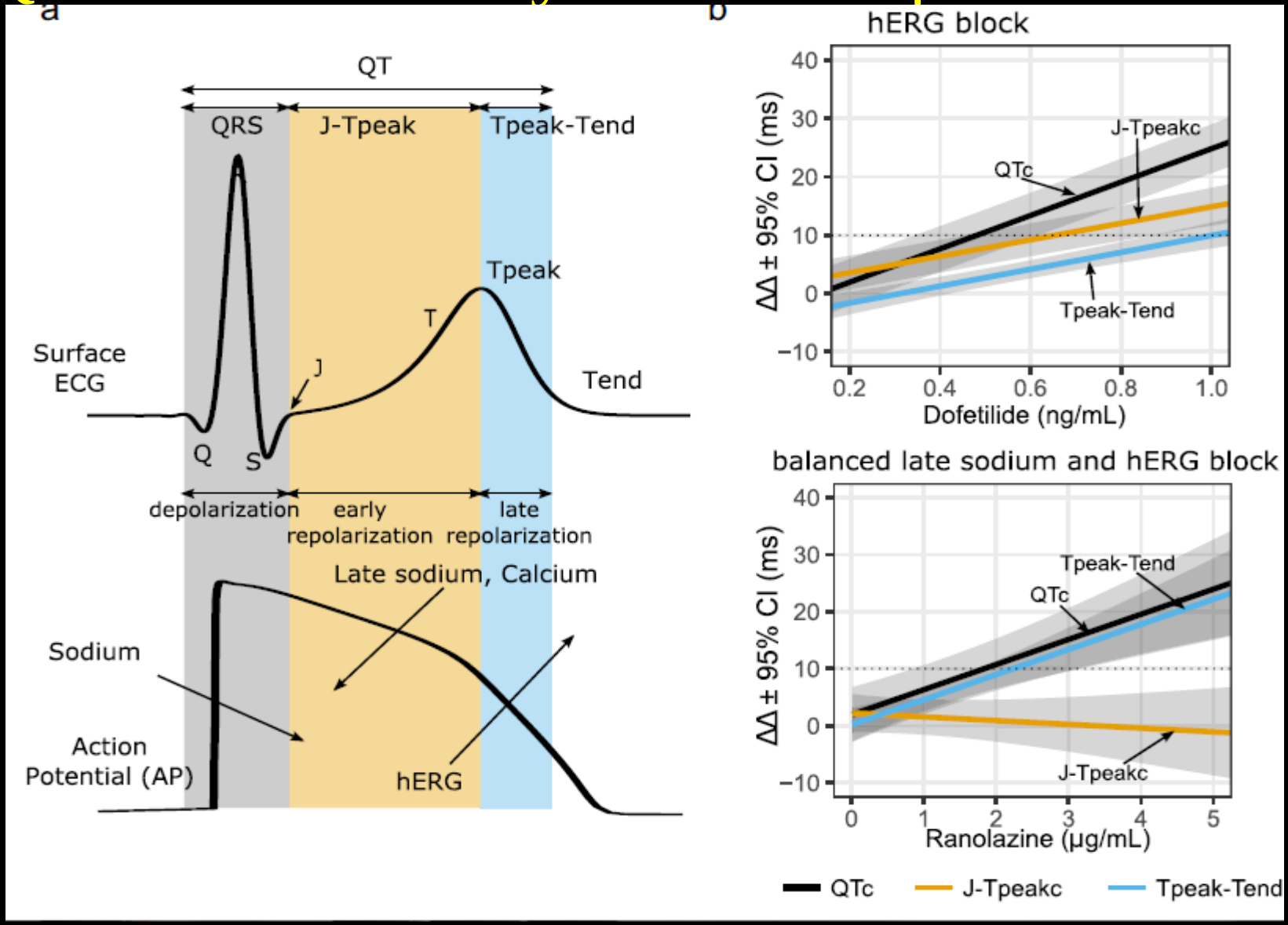
Not all QT prolonging Drugs are Equal

Effect of I_{Kr} *vs* Multichannel Block on QT interval and Risk for TdP



Vicente: *Clin Pharmacol Ther* 2018;103:54-66

Effect of I_{Kr} *vs* Multichannel Block on QT interval – Early vs Late Repolarization

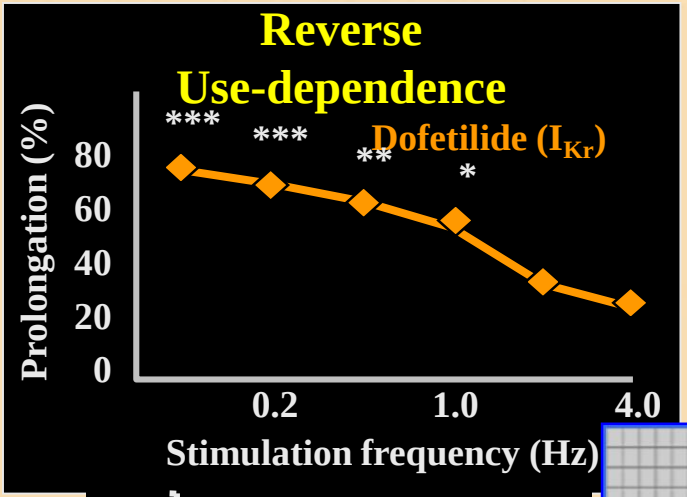


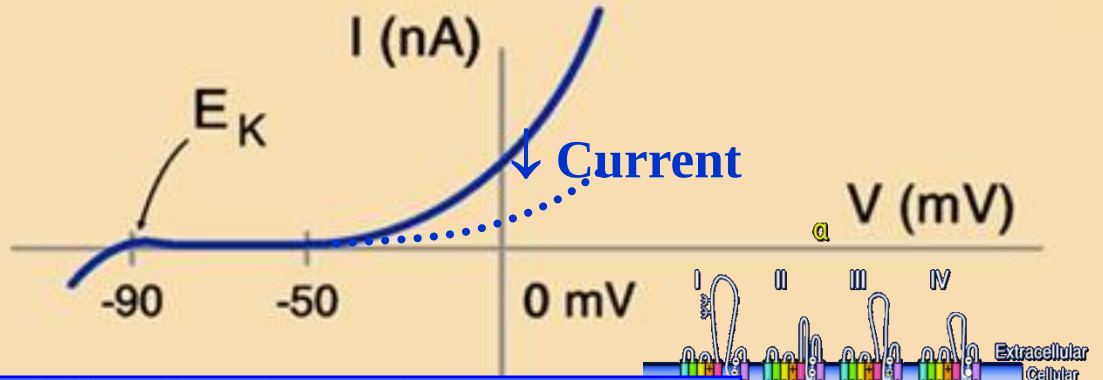
Johannesen: *Clin. Phamacol Ther* 2014;96:549-58

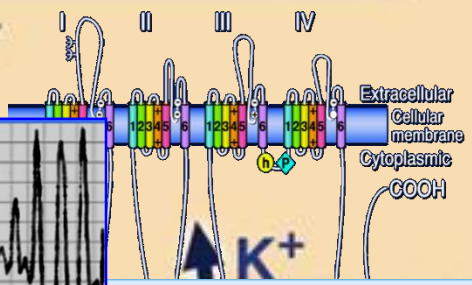
Vicente: *Clin Pharmacol Ther* 2018;103:54-66

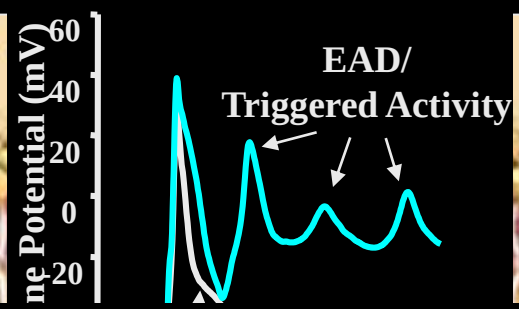
I_{Kr} **Dofetilde, Sotalol**
Erythromycin,

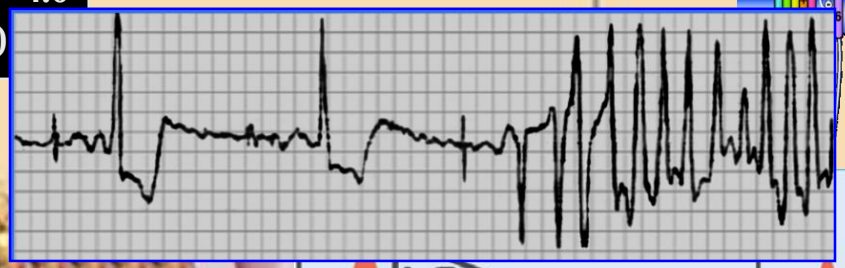
↑ **APD, ERP**
↑ **Refractoriness**
↑ **QT Interval**

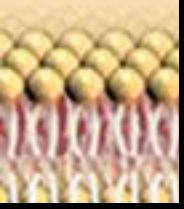


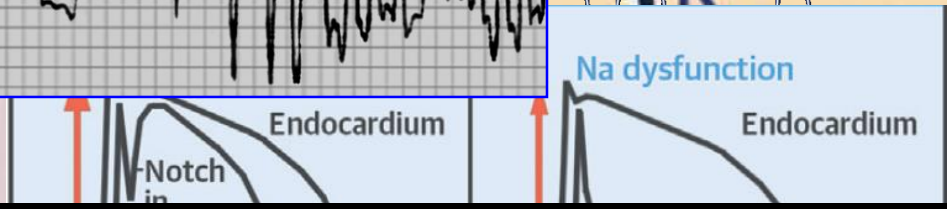












Each 10 ms ↑ in QTc associated with 5-7% ↑ in risk TdP

Drew : Circulation 2010;121:1047-60

The Acquired LQTS: a Genetically Mediated "forme fruste" of Familial LQTS

- "Silent" mutations on LQTS genes
- Mutation Frequency ?
- Alteration in repolarization insufficient to prolong QT at rest, but sensitive to I_K blockade by drugs prolonging APD or hypokalemia triggering TdP

I_{Kr} .. KCNE2 : Q9E (clarithromycin)
I_{Kr} .. KCNH2 : R1047L (dofetilide)
I_{Ks} .. KCNQ1: Y315C (cisapride), MirP1_T8A (sulfa)
I_{Na} .. SCN5A: S1103Y, S1102Y (Af-Am: Amio, Ischemia)

Acquired form of the LQTS in LVH and DCM:
Reduction in I_{to}, I_{K1}, altered Ca^{2+} handling

Drug Interactions Increasing Risk of TdP

- 2 or more QT Prolonging Drugs
  (additive/synergestic effects)

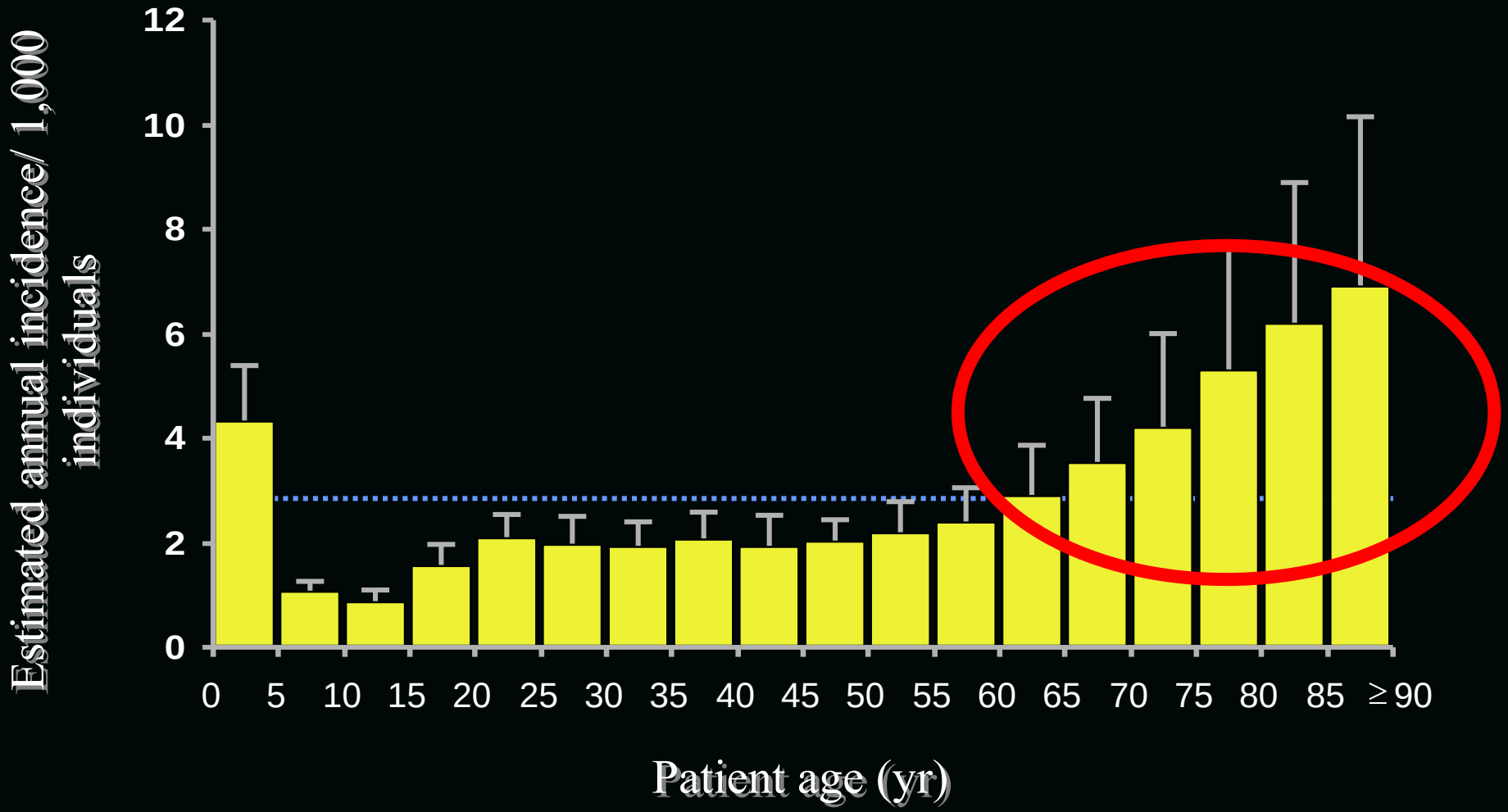
Sotalol + Erythromycin + Antidepressant + Antihistamine

- QT Prolonging Drug + Drug Inhibiting CYP3A4

Dofetilide or Erythromycin + Verapamil + Grape fruit Juice

Diuretic (low K, Mg)

Estimated Annual Incidence of Adverse Drug Events Treated in U.S. Emergency Departments



Budnitz: JAMA 2006;296:1858

Polypharmacy

- older persons take up to 11 different prescribed drugs
  - 2 drugs = 6% risk of interaction
  - 5 drugs = 50% risk of interaction
  - 8 drugs = 100% risk

Identification of Young Patients at Risk for SCD

- Prodromal Symptoms/signs
  - Aborted CA, Exertional Syncope, VT-palpitations
- Screening Test - Monitoring
  - Cost and inconvenience of untargeted screening
  - Sn of test, Disease prevalence, Cost (test, false +ve), Rx
  - ECG, TMET, Echo - ECG Alerts
  - Targeted screening of family members (phenotype, cascade testing)
- Risk Stratification (known cardiac disease)
  - LQTS, HCM, BrS, CPVT, ARVC, LVDysfx
- Risk Factors for drug-induced adverse effects - Alerts
  - Patient-specific, Drug-specific (dofetilide, sotalol)
    Dynamic factors (repolarization reserve - drug-drug-disease interaction) - ECG Alerts

21-y/o Female with Syncope

- Does she has a LQTS channelopathy or was the episode primarily related to erythromycin effect on cardiac repolarization?
- Is she at high risk for cardiac arrhythmias and sudden cardiac death?
- Does she need an ICD for prevention of SCD?
- Are other family members at risk of cardiac arrhythmias?
- What advice should be given with regard to exercise, sports activity, pregnancy.