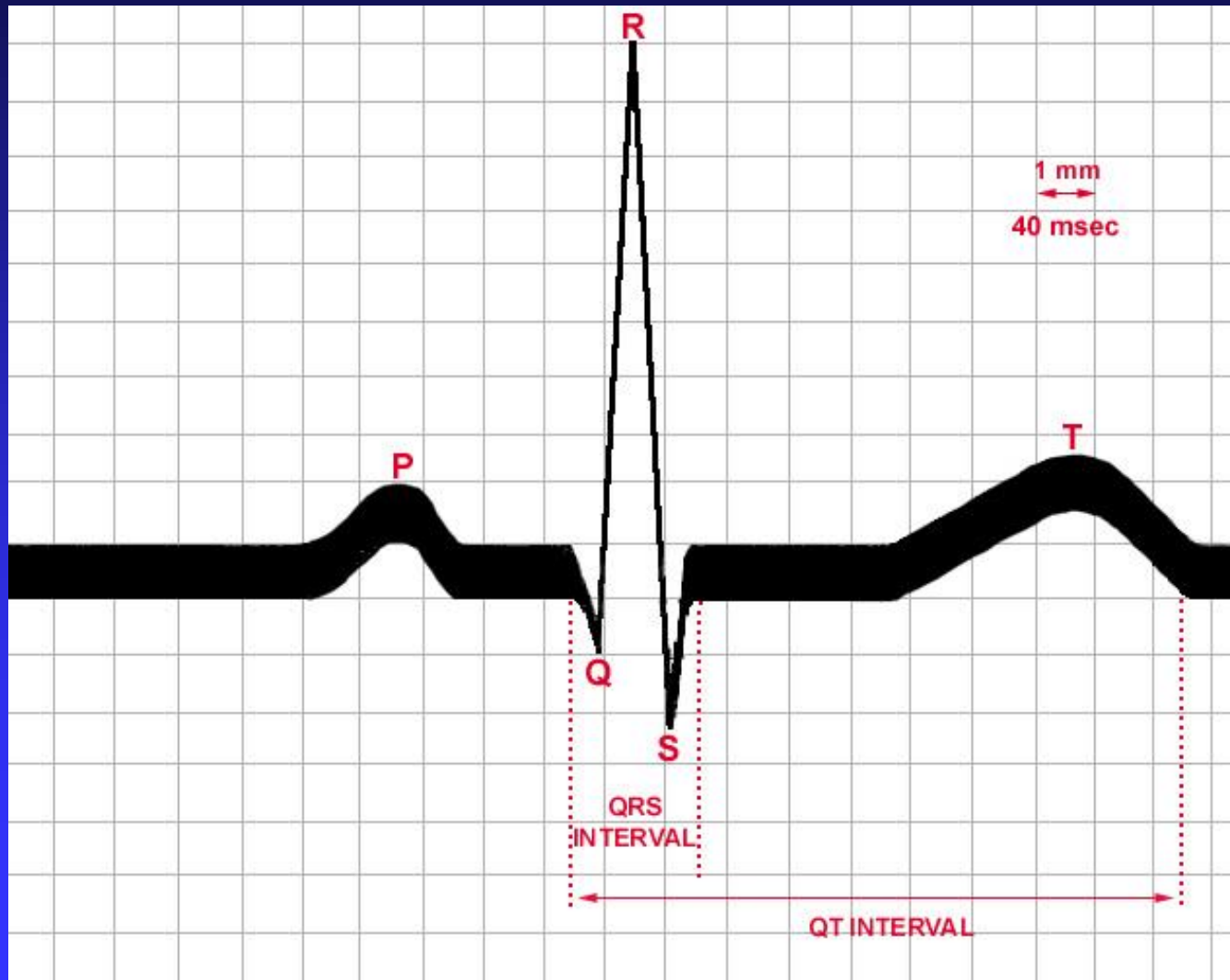


Drugs Prolonging QT Interval

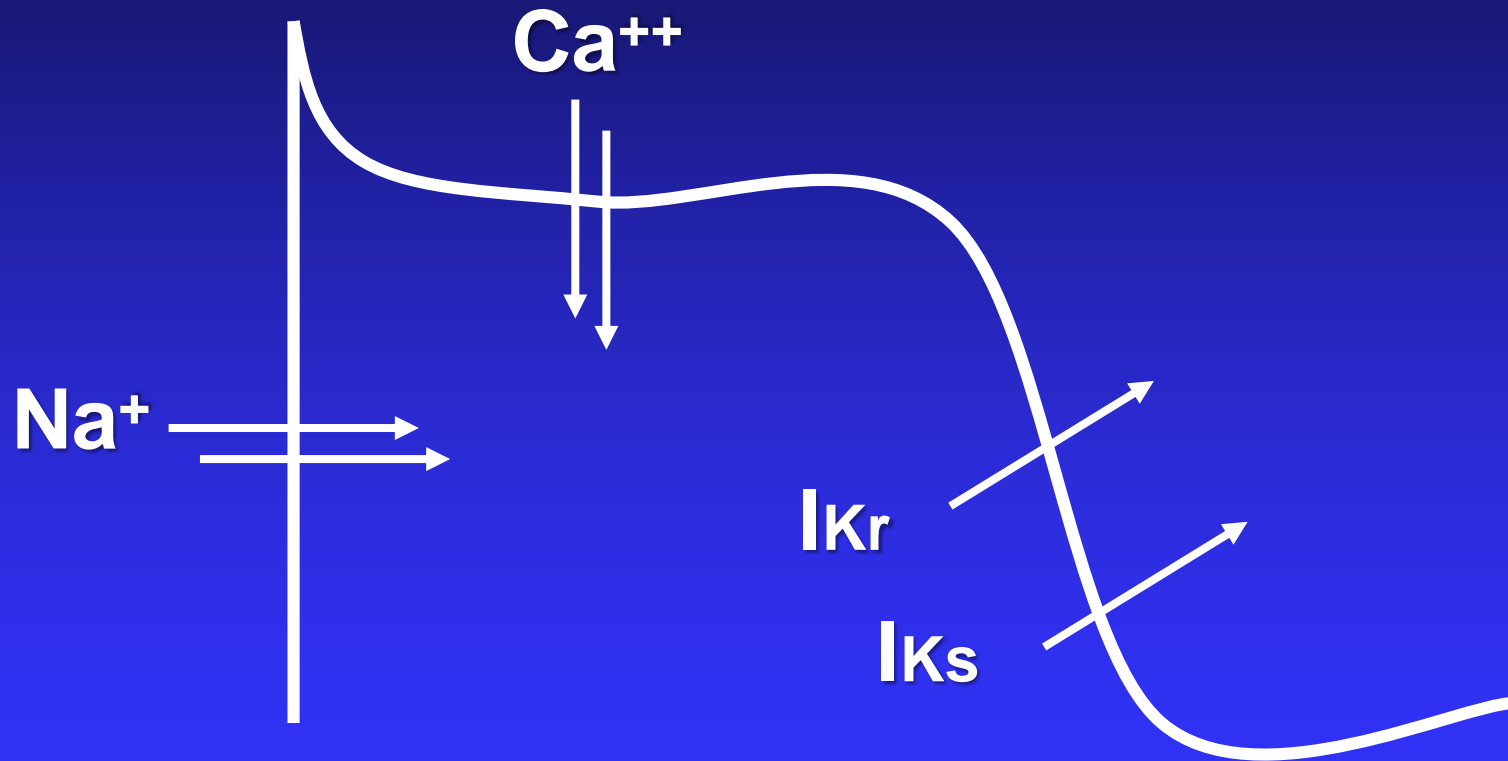
Wojciech Zareba, MD, PhD
Professor of Medicine/Cardiology

University of Rochester Medical Center
Rochester, NY

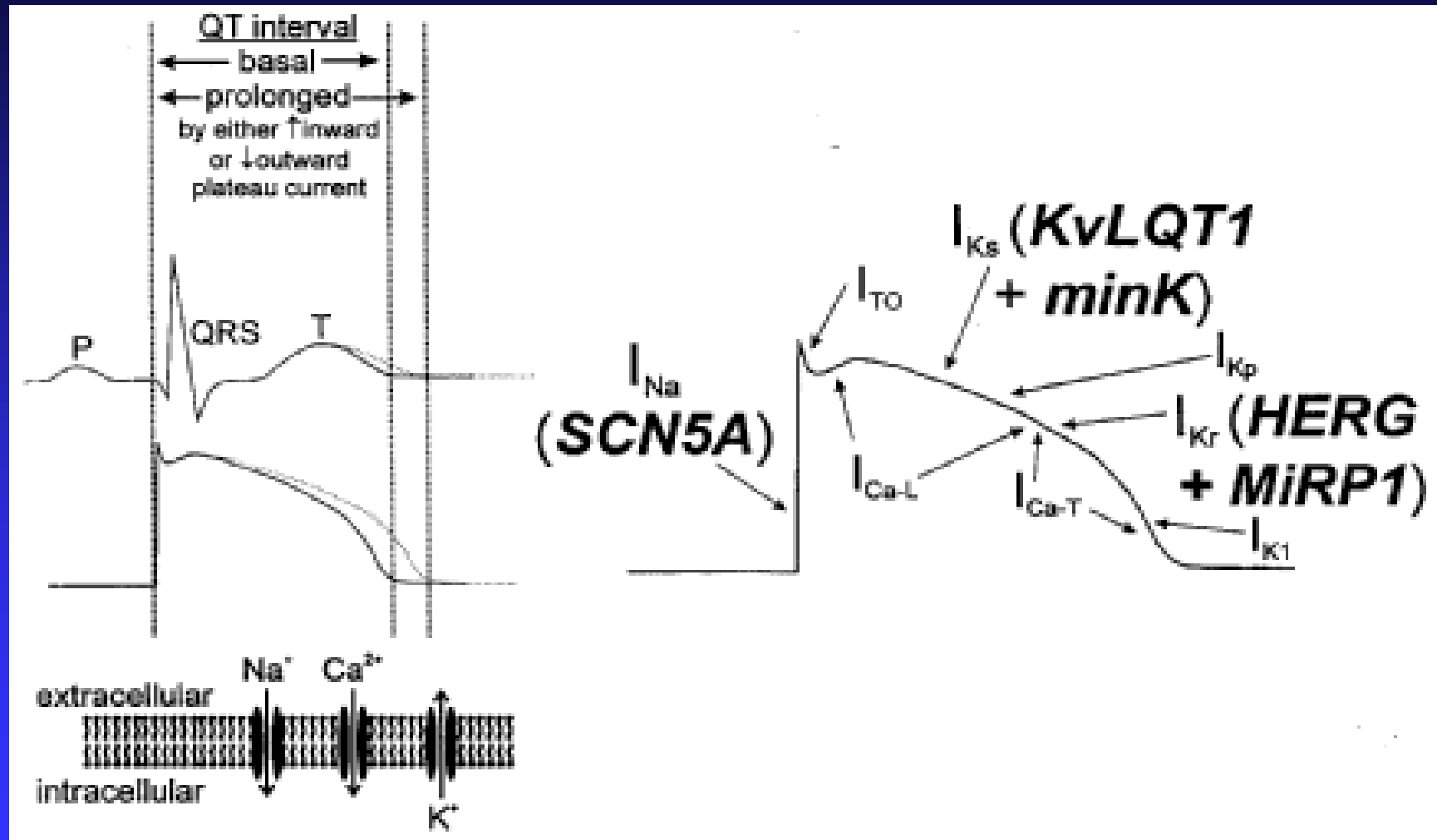
ECG - QT Interval



Ventricular Action Potential



LQTS: Genes & Channels



QT Prolongation & Torsades de Pointes

- ◆ Congenital LQTS
- ◆ Acquired LQTS
 - ◆ **Drugs**
 - ◆ Bradycardia
 - ◆ Hypokalemia
 - ◆ CHF & LVH

Drugs that prolong the QT interval

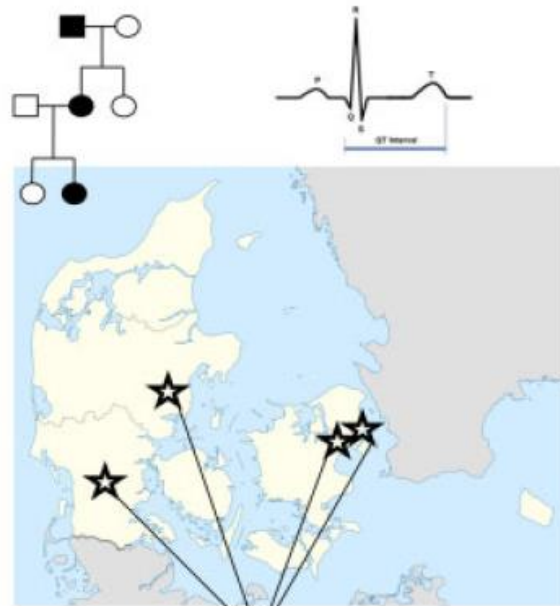
Category	Drugs
Antihistamines	Astemizole, terfenadine
Anti-infectives	Amantadine, clarithromycin, chloroquine, erythromycin, grepafloxacin, moxifloxacin, pentamidine, sparfloxacin, trimethoprim-sulfamethoxazole
Antineoplastics	Tamoxifen
Antiarrhythmics	Quinidine, sotalol, procainamide, amiodarone, bretylium, disopyramide, flecainide, ibutilide, moricizine, tocainide, dofetilide
Antilipemic agents	Probucol
Calcium channel blockers	Bepridil
Diuretics	Indapamide
Gastrointestinal agents	Cisapride
Hormones	Fludrocortisone, vasopressin
Antidepressants	Amitriptyline, amoxapine, clomipramine, imipramine, nortriptyline, protriptyline
Antipsychotic	Chlorpromazine, haloperidol, perphenazine, quetiapine, risperidone, sertindole, thioridazine, ziprasidone, doxepin, methadone

Drugs Withdrawn for TdP

<u>Drug</u>	<u>Class</u>	<u>Date Withdrawn</u>
Terfenadine	Antihistamine	Feb 1998
Sertindole	Antipsychotic	Dec 1998
Astemizole	Antihistamine	Jun 1999
Grepafloxacin	Antibiotic	Nov 1999
Cisapride	GI Prokinetic	July 2000

Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality

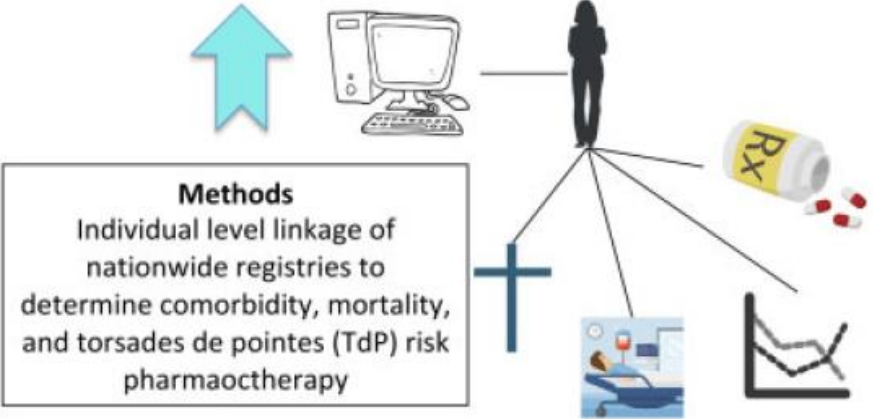
Weeke et al. Eur Heart J 2019



Study population
279 patients with Congenital Long QT Syndrome (cLQTS) identified from 4 inherited cardiac disease clinics in Denmark

Findings

- 60% of all cLQTS patients were treated with a TdP risk drug *after* cLQTS diagnosis
- Treatment with TdP risk drugs decreased 1 year after cLQTS diagnosis
- Risk factors for TdP risk drug treatment after cLQTS diagnosis were increasing age and previous TdP risk drug treatment
- During follow-up, nine patients were admitted with ventricular arrhythmia (three were in treatment with a TdP risk drug) and eight patients died (four were in treatment with a TdP risk drug)



Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality

Weeke et al. Eur Heart J 2019

The most common prescriptions used after LQTS diagnosis in 167 patients

Antibiotics	57 (34%)
Antidepressants	20 (12%)
Antifungals	17 (10%)
PPI	25 (15%)

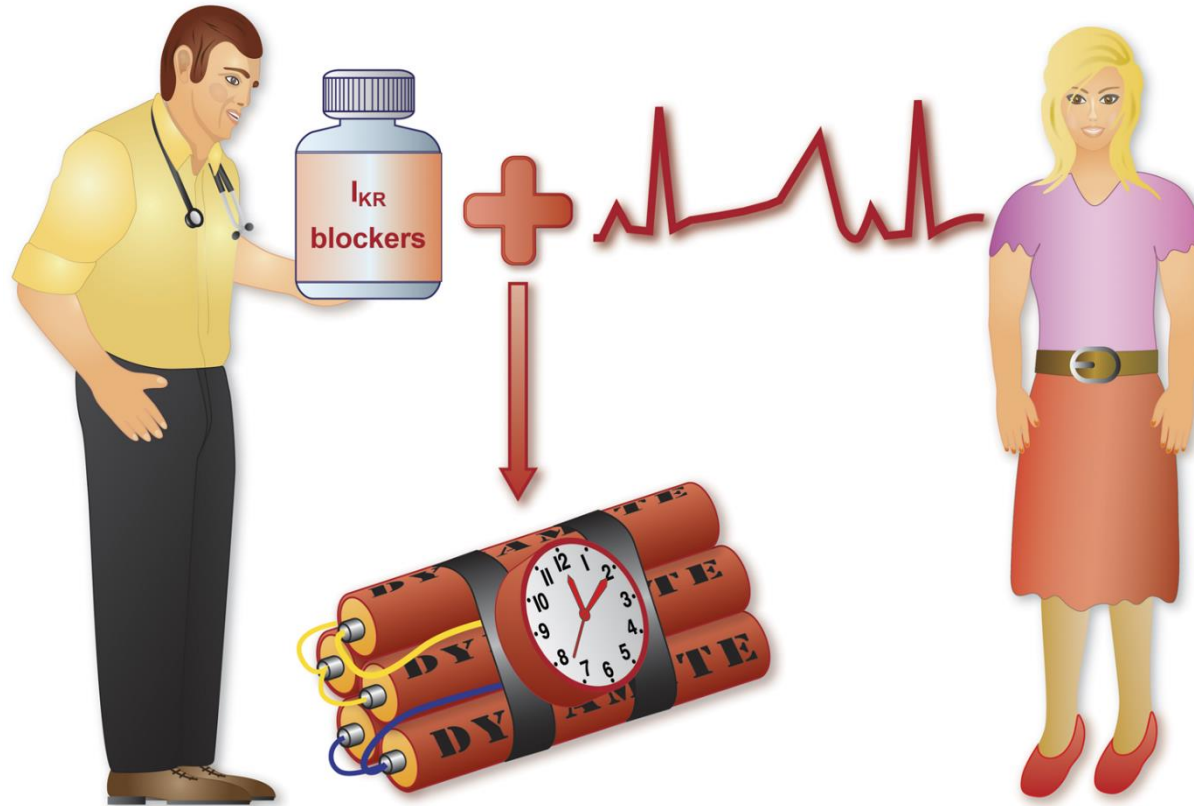
Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality

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When doctors prescribe a drug with an I_{Kr} blocking activity, or any other QT prolonging action, to patients affected by the long QT syndrome they are in essence presenting them with a potential time bomb which may, or may not explode in a near or distant future.



Search for Drugs that Prolong QT & induce Torsades de Pointes (TdP)

Based on ongoing systematic analysis of all available evidence, CredibleMeds® places drugs into broad categories based on whether each can cause QT prolongation or TdP. These actions are highly dependent on the circumstances of each drug's use AND each patient's clinical characteristics.

Search for Drug of Interest:

Search

QT/TdP Risk Categories for Drugs



Known Risk of TdP - These drugs prolong the QT interval **AND** are clearly associated with a known risk of TdP, even when taken as recommended.



Possible Risk of TdP - These drugs can cause QT prolongation **BUT** currently lack evidence for a risk of TdP when taken as recommended.



Conditional Risk of TdP - These drugs are associated with TdP **BUT** only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).



Drugs to Avoid in Congenital Long QT Syndrome (cLQTS) - These drugs pose a high risk of TdP for patients with cLQTS and include all those in the above three categories (KR, PR & CR) **PLUS** additional drugs that do not prolong the QT interval per se but which have a Special Risk (SR) because of their other actions.

CredibleMeds.org



Known Risk: These drugs should only rarely, if ever, be given to patients with CLQTS because the danger is clear. However, when no alternative safe drug is available and the illness is severe, some patients with CLQTS may be treated by physicians with expertise in the treatment of arrhythmias.



Possible Risk: These drugs have been found to increase QT intervals in some patients and for that reason could theoretically be dangerous in CLQTS. However, if the drugs are medically necessary, they may be prescribed by medical specialists for patients with CLQTS.



Conditional Risk: Most of these can be prescribed safely for many patients with CLQTS because the drug's risk is confined to certain conditions, e.g. overdose, excessive duration of treatment, use with diuretics or drugs that block their elimination, or patients with other risk factors.

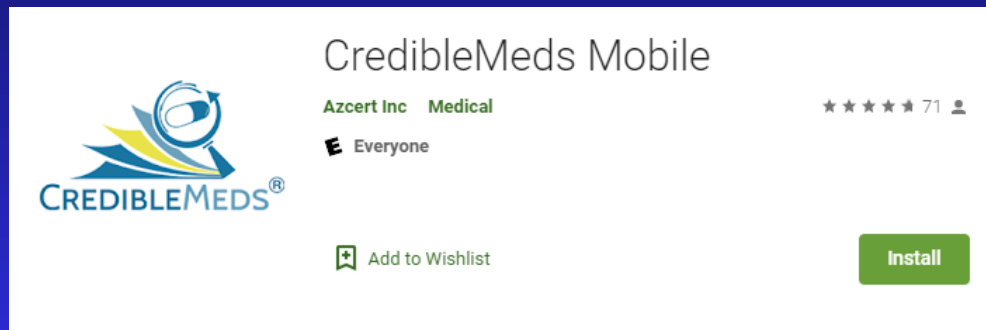


Special Risk: These drugs have a theoretical risk of causing arrhythmias in some CLQTS patients because they have adrenaline-like effects. Many of these medicines are necessary for treatment of asthma, ADHD or nasal congestion. Physicians with expertise in the treatment of arrhythmias may prescribe these medicines to carefully selected patients with CLQTS.

Table 2 The most common first claimed prescriptions associated with risk of TdP after time of cLQTS diagnosis

	N (%)	TdP risk category
Any QT risk drug	167	
Analgesics	15 (9.0)	
Tramadol	14 (8.4)	Possible risk
Antibiotics	57 (34.1)	
Azithromycine	11 (6.6)	Known risk
Clarithromycine	7 (4.8)	Known risk
Erythromycine	5 (3.0)	Known risk
Roxithromycine	20 (12.0)	Known risk
Metronidazole	14 (8.3)	Conditional risk
Proton-pump inhibitors	25 (15.0)	
Esomeprazole	6 (3.6)	Conditional risk
Lanzoprazole	10 (6.0)	Conditional risk
Omeprazole	5 (3.0)	Conditional risk
Pantoprazole	4 (2.4)	Conditional risk
Antidepressants	20 (12.0)	
Citalopram	8 (4.8)	Known risk
Sertraline	5 (3.0)	Conditional risk
Escitalopram	3 (1.8)	Known risk
Antifungals	17 (10.2)	
Fluconazole	17 (10.2)	Known risk

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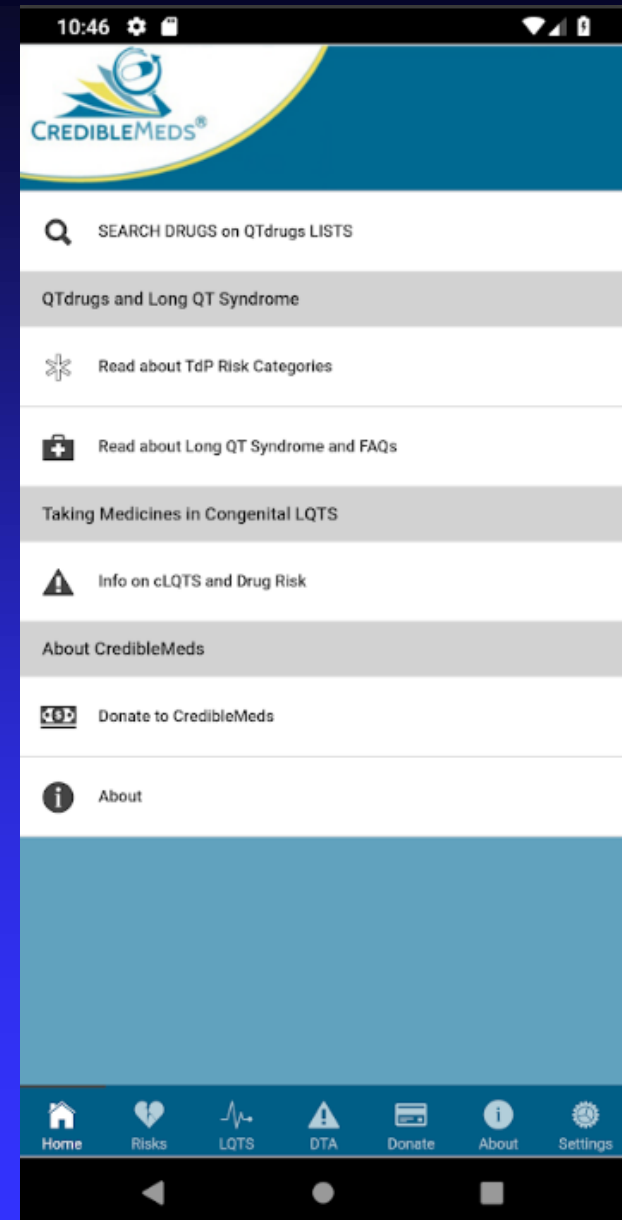
Azcert Inc Medical

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SEARCH DRUGS on QTdrugs LISTS

QTdrugs and Long QT Syndrome

- Read about TdP Risk Categories
- Read about Long QT Syndrome and FAQs

Taking Medicines in Congenital LQTS

- Info on cLQTS and Drug Risk

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September 15, 2019

Dear subscribers to CredibleMeds.org:

The following drugs have been added to the **Possible Risk of TdP** list because we have found evidence of QT prolongation with their use but, at this time, we have not found convincing evidence of torsades de pointes (TdP).

Levomethadone (used to treat narcotic addiction)

Lefamulin (Antibiotic to treat community acquired pneumonia)

Pretomanid (Drug for extensively drug-resistant TB)

Entrectinib (Anti-cancer drug)

Pitolisant (Drug for treatment of narcolepsy/daytime sleepiness)

Also, **Risperidone**, a medicine used to treat psychosis and other conditions, has been moved from the Possible Risk of TdP list to the **Conditional Risk of TdP** list because it has been associated with reports of TdP in conditions such as: bradycardia (slow heart rate), low serum potassium, low serum magnesium, excessive dose or when taken with other drugs that prolong QT.

Abiraterone, a drug for prostate cancer has been added to the **Conditional Risk of TdP** list because it has been associated with low serum potassium and reports of TdP.

All of the above medicines and the asthma medicines, **Fenoterol** and the inhaled bronchodilator/corticosteroid combination **Salmeterol/fluticasone**, were added to the **Drugs to Avoid in congenital Long QT syndrome (cLQTS)** category.

We welcome your feedback and suggestions for how CredibleMeds can better serve your need for information about medicines.

Remember, the CredibleMeds mobile app for the QTdrugs lists can be obtained free by clicking these links to the Apple App Store (iOS) and Google Play (Android devices).

Grapefruit juice prolongs the QT interval of healthy volunteers and patients with long QT syndrome

Chorin et al. Heart Rhythm J 2019;16:1141-48

