# Treatment of torsades de pointes due to long QT syndrome

**Acquired LQTS**

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**Congenital LQTS**

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Acquired long QT syndrome

INTRODUCTION — The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) (waveform 1) [1-3]. This syndrome is associated with an increased risk of a characteristic life-threatening cardiac arrhythmia, known as torsades de pointes (TdP) (waveform 2A-B) [4,5]. The primary symptoms in patients with LQTS include palpitations, syncope, seizures, and sudden cardiac death (SCD).

The long QT syndrome may be either genetic or acquired [6-9]. Acquired LQTS usually results from drug therapy, hypokalemia, or hypomagnesemia (table 1). As will be described below, hypokalemia, hypomagnesemia, and bradycardia can increase the risk of drug-induced LQTS. In addition, some patients with acquired LQTS have an underlying "forme fruste" of congenital LQTS. (See 'Mutations in LQTS genes' below.)

The pathophysiology, causes, and management of acquired LQTS will be reviewed here. The clinical manifestations of acquired LQTS are similar to those in congenital disease and are discussed elsewhere. (See "Clinical features of congenital long QT syndrome").

TORSADES DE POINTES — Torsades de pointes (TdP) is a form of polymorphic ventricular tachycardia (VT) that occurs in the setting of acquired or congenital QT interval prolongation [4,5]. Polymorphic VT is defined as a ventricular rhythm faster than 100 beats per min with frequent variations of the QRS axis, morphology, or both [5,6]. In the specific case of TdP, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis (waveform 2A-B). The peaks of the QRS complexes appear to "twist" around the isoelectric line of the recording; hence the name torsades de pointes or "twisting of the points".

Typical features of TdP include an antecedent prolonged QT interval, particularly in the last sinus beat preceding the onset of the arrhythmia, a ventricular rate of 160 to 250 beats per minute, irregular RR intervals, and a cycling of the QRS axis through 180 degrees every five to 20 beats [5,6]. TdP is usually short-lived and terminates spontaneously. However, most patients experience multiple episodes of the arrhythmia, and episodes can recur in rapid succession, potentially degenerating to ventricular fibrillation and SCD [5,6].

PATHOPHYSIOLOGY — The pathophysiology of LQTS is described in detail elsewhere. The proposed mechanism for drug-induced TdP is the development of early afterdepolarizations and triggered activity resulting from prolonged repolarization. (See "Pathophysiology of the long QT syndrome").
There are thought to be pathophysiologic differences between the acquired and congenital forms of the LQTS:

- The polymorphic VT in the acquired form of LQTS is most commonly precipitated by short-long RR intervals. This interval typically is caused by a ventricular premature beat followed by a compensatory pause (waveform 2B). Polymorphic VT also can occur in association with bradycardia or frequent pauses; as a result, the acquired form of LQTS is sometimes called "pause-dependent" LQTS [3].

The association between bradycardia and antiarrhythmic drug-induced TdP is thought to be related to a property of some of these drugs called "reverse use dependence," which is defined as the inverse correlation between the heart rate and QT interval [10]. As a result, the QT interval decreases as the heart rate increases and lengthens as the heart rate slows. This explains why drug-induced torsades de pointes is more commonly seen with bradycardia.

Reverse use dependence may be mediated at least in part by changes in the extracellular potassium concentration. Virtually all of the drugs that produce LQTS act by blocking the outward IKr current, which is mediated by the potassium channel encoded by the HERG gene [11-30]. The degree of drug blockade of IKr, the rapid component of the delayed rectifier potassium current that is responsible for phase 3 depolarization, is inversely related to both the extracellular potassium concentration and heart rate [13]. Lower heart rates result in less potassium moving out of the cell during repolarization (before subsequent reuptake by the Na-K-ATPase pump), since there are fewer repolarizations. The associated reduction in extracellular potassium concentration enhances the degree of drug-induced inhibition of IKr, increasing the QT interval [13].

- In contrast to the association with bradycardia and pauses seen in acquired LQTS, arrhythmias often follow a sudden adrenergic surge (due, for example, to exercise or arousal) in some congenital forms of LQTS, particularly LQTS types 1 and 2 (figure 1). (See "Clinical features of congenital long QT syndrome", section on "Triggers of arrhythmia").

However, these distinctions between acquired and congenital LQTS are not absolute. This was illustrated in an observational study of 15 patients with congenital LQTS in which "pause-dependent" TdP, which is more characteristic of the acquired form, was noted in 14 [31]. (See "Pathophysiology of the long QT syndrome").

**DRUG-INDUCED TdP** — Drugs are a common cause of acquired LQTS and TdP. Many drugs have been implicated, and additional medications continue to be identified [9,32,33]. The major classes of drugs that prolong the QT interval include (table 1)[32,34-38]:

- Antiarrhythmic drugs
- Certain non-sedating antihistamines (eg, terfenadine and astemizole)
- Macrolide antibiotics
- Certain psychotropic medications
- Certain gastric motility agents (eg, cisapride)

Determining the absolute and comparative risk of the many drugs associated with QT prolongation is difficult, since most available data comes from case reports or small observational series.

Some drugs have been taken off the market in the United States and other countries because they increase the risk of TdP (eg, cisapride, terfenadine, astemizole). An internet resource with updated lists of

specific drugs that prolong the QT interval is available at the University of Arizona Center for Education and Research on Therapeutics website (www.qtdrugs.org).

**Importance of HERG blockade** — Virtually all of the drugs that produce LQTS act by blocking the IKr current mediated by the potassium channel encoded by the HERG gene [11-30]. In addition, one of the forms of congenital LQTS, LQTS type 2, is due to mutations in HERG. (See "Genetics of congenital and acquired long QT syndrome").

The relationship between the degree of drug-induced HERG blockade and the risk of ventricular arrhythmias and sudden cardiac death was described in a report from the International Drug Monitoring Program of the World Health Organization [39]. For 52 medications associated with QT prolongation and TdP, the investigators compared the plasma concentrations achieved during usual clinical use, defined as the effective free therapeutic plasma concentration (ETCP), to the in vitro concentration of the drug that inhibits 50 percent of potassium channels (IC50). The ratio of these values (ETCP/IC50) is considered a measure of the therapeutic/toxic window. The following findings were reported:

- The ETCP/IC50 ratio ranged from 0.00003 for nifedipine (indicating that drug levels in general clinical use are substantially lower than levels required to block potassium channels), to 29.7 for thioridazine (indicating that usual drug levels have significant potassium channel blocking activity).
- Eight medications had a ratio >1, including cisapride, sparfloxacin, quinidine, ibutilide, and thioridazine.
- There was a linear relationship between the ETCP/IC50 ratio and the reported incidence of a composite end point of cardiac arrest, sudden death, TdP, ventricular tachycardia, and ventricular fibrillation.

**Incidence with specific drugs** — The incidence of drug-induced TdP is difficult to estimate and may be higher than suggested by documented cases. This possibility was illustrated in an observational study of 500,000 persons in the Netherlands [40]. In this cohort, 775 cases of SCD were identified over a period of slightly less than nine years, and each case was matched to up to 10 controls. The following findings were noted:

- Current use of any non-cardiac QT prolonging drug was associated with a significantly increased risk of SCD (adjusted OR 2.7), and the highest risk was associated with antipsychotic drugs (adjusted OR 5.0).
- The risk was higher in women and in people who had recently started a QT prolonging drug.
- Past use of a QT prolonging drug was not associated with SCD (OR 0.9).

Although these results suggest that drug-induced TdP may be more common than documented cases suggest, the absolute number of events is still low and represents a small proportion of SCD events (24 of 775 patients with SCD [3.1 percent] were currently using a QT prolonging drug).

The relative frequency of the different causes of drug-induced TdP will vary with the population studied and the drugs that are available (eg, cisapride is not easily available in the United States but is available in some other countries). The range of findings can be illustrated by the following observations:

- Among 761 cases of drug-induced TdP reported to the World Health Organization Drug Monitoring Centre between 1983 and 1999, the most common drugs were sotalol and cisapride (17 and 13
percent) [32].

- In a review of 92 patients from the United States with drug-induced TdP, antiarrhythmic drugs were responsible in 71 (77 percent) [34].

Among drugs still available in the United States, some of the best data on incidence of TdP come from studies of antiarrhythmic drugs, particularly class IA and class III drugs, and psychotropic medications.

**Antiarrhythmic drugs**

- **Quinidine**, a class IA sodium channel blocking agent, has been the most frequently implicated cause of drug-induced TdP, with an incidence of 0.6 to 1.5 percent [41]. Most cases occur within 48 hours of initiating drug therapy; associated factors are hypokalemia and excessive bradycardia. The incidence may be reduced by careful attention to correction of hypokalemia or hypomagnesemia before therapy and discontinuation of drug therapy if QT prolongation occurs [42]. Although quinidine-induced QT prolongation and TdP ("quinidine syncpe") often are dose-related, these abnormalities may represent an idiosyncratic reaction, occurring when drug dose and serum concentrations are low. However, even low serum concentrations of quinidine can block the HERG channel [39]. Proarrhythmia may lead to increased mortality when quinidine is used to maintain sinus rhythm after cardioversion in patients with atrial fibrillation [43].

- Although TdP occurs with **disopyramide** and **procainamide** (also class IA), the incidence is unknown but probably lower than seen with **quinidine** [44,45]. With procainamide therapy, it is likely that QT prolongation and TdP result from the major metabolite of the drug, N-acetylprocainamide (NAPA), which has class III potassium channel blocking activity and therefore causes QT prolongation [46]. This complication may be more common in patients who rapidly metabolize procainamide by acetylation (ie, rapid acetylators) and have high NAPA levels.

- **Sotalol** (class III) causes QT prolongation and TdP in approximately 2 percent of men and 4 percent of women [47,48]. Unlike **quinidine**, these complications usually are related to the dose and blood level [49]. As a result, sotalol therapy should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment.

- **Dofetilide** (class III) was associated with TdP in two major trials in 0.9 percent of patients with a recent myocardial infarction and left ventricular dysfunction and in 3.3 percent of patients with heart failure [50,51]. The majority of episodes occurred within the first three days, the time of peak increase in the QT interval [51]. As a result, patients must be **hospitalized** for a minimum of three days for dofetilide initiation at a facility that can provide measurement of creatinine clearance, cardiac monitoring, and cardiac resuscitation.

- Proarrhythmia is the most common toxic reaction with intravenous **ibutilide** (class III); such arrhythmias include nonsustained polymorphic ventricular tachycardia (2.7 percent of patients), sustained polymorphic VT (1.7 percent), nonsustained monomorphic VT (4.9 percent), and sustained monomorphic VT (0.2 percent) [52,53]. One study also found an association between sustained TdP and a history of heart failure or low ejection fraction. Sustained TdP occurred in 5.4 percent versus 0.8 of patients with and without heart failure, respectively.

- **Amiodarone** (class III) markedly prolongs the QT interval. However, in contrast to the other class III antiarrhythmic drugs, amiodarone is rarely associated with TdP, except when used concomitantly with a class IA agent or when hypokalemia is present [54]. The estimated incidence of TdP is less
than 1 percent overall [55] and, in a review of 738 patients in randomized trials of low-dose therapy (≤400 mg/day for at least one year, there were no cases of TdP [56]. Several factors contribute to the rarity of TdP with amiodarone: lack of reverse use dependence; concurrent blockade of the L-type calcium channels; and less heterogeneity of ventricular repolarization (less QT dispersion). (See "Major side effects of amiodarone", section on 'Cardiac toxicity'.)

Data are not as readily available on the incidence of TdP with drugs other than antiarrhythmic medications, most of which are used for noncardiac reasons and in much less controlled settings than antiarrhythmic drugs (table 1). Furthermore, patients taking these drugs are less likely to also be taking drugs that produce hypokalemia and/or hypomagnesemia than those with arrhythmias.

**Psychotropic medications**

- **Haloperidol** was the topic of a United States Food and Drug Administration (FDA) alert in September 2007, based upon the observation that QT prolongation and TdP have been observed in patients receiving haloperidol, especially when it is administered intravenously or in higher doses than recommended. Because of the widespread use of haloperidol and also the potential confounding influence of other QT-prolonging factors, the magnitude of the risk associated with or attributable to haloperidol cannot be determined from the case reports upon which this advisory was based. However, a direct effect is likely since in vitro studies have shown that haloperidol is a high-potency blocker of the HERG channel that is blocked by virtually all drugs that cause LQTS [29]. (See 'Importance of HERG blockade' above.)

The FDA observed that, although cases of QT prolongation and TdP have been reported in the absence of other predisposing factors, particular caution should be exercised in treating patients with haloperidol who have any of the following characteristics:

- Electrolyte abnormalities (particularly hypokalemia or hypomagnesemia)
- Use of other drugs known to prolong the QT interval
- Congenital long QT syndrome
- Underlying cardiac abnormalities
- Hypothyroidism

The FDA also recommended ECG monitoring when haloperidol is given intravenously. Furthermore, the FDA observed that haloperidol is approved for intramuscular, but not intravenous use. Off-label intravenous use is common, however, and it is not clear if the route of administration affects the risk of QT prolongation and TdP.

Although typical antipsychotic drugs like haloperidol and thioridazine have received particular attention with regard to risk of arrhythmia and sudden death, there is evidence that several atypical antipsychotic medications can prolong the QT interval and cause TdP [57]. In addition, a large retrospective cohort study found that treatment with typical and atypical antipsychotics was associated with similar increases in the risk of sudden death in patients with psychosis [58]. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and comparative side effects").

- **Methadone** often increases the QTc interval and is a cause of TdP. Concern regarding the proarrhythmic potential of methadone prompted a clinician safety alert from the FDA in 2006, as
well as a manufacturer's black-box warning. These issues as well as safety recommendations for prescribing methadone are discussed elsewhere. (See "Treatment of opioid abuse and dependence", section on 'Cardiac arrhythmias'.)

**Other medications**

- Cisapride, which is not easily available in the United States, has been one of the most common causes of acquired TdP not due to antiarrhythmic drugs [32]. The proarrhythmic effect of cisapride in children was prospectively evaluated in 35 children (mean age 5.2 years) with gastroesophageal reflux disease [59]. Prolongation of the corrected QT interval (QTC) occurred in 11 (31 percent), two of whom (5.7 percent of the whole group) developed TdP.

- Users of erythromycin had a twofold increased risk of sudden cardiac death over nonusers in one report [60]. In addition, because erythromycin is metabolized by the CYP3A4 system, medications that inhibit CYP3A4 cause a further increase in risk when used with erythromycin (table 2). In an analysis of over one million patient-years of follow-up data, those using diltiazem, verapamil, troleandomycin, or azole antifungal drugs (all of which inhibit CYP3A4) had a five-fold increase in sudden cardiac death risk when taking erythromycin [60].

- Arsenic trioxide is a newer drug used in the treatment of patients with acute promyelocytic leukemia and other advanced malignancies. It appears to be associated with a very high rate of QT prolongation but a lower rate of TdP [61-63]. In an initial report, all eight patients treated with arsenic trioxide developed QT prolongation and four developed nonsustained ventricular tachycardia requiring treatment with antiarrhythmic agents [62]. A lower but still high risk was noted in a much larger series of 99 patients [61]. Reversible prolongation of the QT interval to more than 0.50 sec occurred in 38 patients; the risk was increased in patients with hypokalemia, and one hypokalemic patient developed TdP.

The unusually high incidence of QT prolongation with arsenic trioxide may be a consequence of a unique effect on potassium flux. As noted above, most of the drugs that produce LQTS act by blocking the IKr current. However, arsenic trioxide blocks both IKr and IKs, an effect comparable to the combined effects of genetic LQT1 and LQT2 [64]. This effect may be mitigated somewhat because arsenic trioxide also activates IK-ATP, another outward potassium current.

Labeling instructions for arsenic trioxide recommend that, during therapy, serum potassium concentrations should be kept above 4 meq/L and magnesium concentrations above 1.8 mg/dL [61,65]. In addition, serial ECGs should be obtained and the patient should be hospitalized and placed on telemetry if the QT interval is greater than 0.50 sec or the patient develops palpitations or syncope [61].

**Risk factors** — Although drug-induced TdP is sometimes regarded as an idiosyncratic event, a number of risk factors have been identified [11,35,66]. Patients with multiple risk factors may face the greatest risk [66]. These factors can be classified as follows.

With respect to the drug regimen:

- High drug doses or concentrations of QT prolonging drug (quinidine is an exception); thioridazine, for example, should be limited to doses ≤100 mg/day [67].
- Rapid intravenous infusion of QT prolonging drug.

- Concurrent use of more than one drug that can prolong the QT interval or use of a QT prolonging drug with one that slows drug metabolism due to inhibition of hepatic cytochrome P450 enzymes, such as erythromycin (which also directly causes QT prolongation) [19,20,24,60], and cimetidine [58]; in addition, concurrent intake of grapefruit juice, which inhibits CYP3A4, can increase the QT interval by two possible mechanisms: slowed metabolism of other drugs and direct inhibition of the IKr channel by flavonoids in grapefruit juice [59].

- Diuretic treatment may be a risk factor due to its correlation with electrolyte abnormalities and heart failure or due to the direct blockade of potassium current by some diuretics [66].

With respect to ECG abnormalities:

- Baseline QT prolongation or T wave lability

- The development of marked QT prolongation (eg. QTc >500 ms), T wave lability, or T wave morphologic changes (such as LQT2-type repolarization: notching, long T peak-Tend) during therapy

- Bradycardia which, as noted above, may be related to a fall in local extracellular potassium concentration, leading to enhanced drug-induced inhibition of IKr [13]
  - Sinus bradycardia, heart block, incomplete heart block with pauses
  - Premature complexes leading to short-long-short cycles

- Congenital long QT syndrome or "silent" mutations in LQTS genes (see 'Mutations in LQTS genes' below)

With respect to metabolic factors:

- Electrolyte disturbances, especially hypokalemia and hypomagnesemia and less often hypocalcemia

- Impaired hepatic and/or renal function

Clinically silent risk factors [66]:

- Occult (latent) congenital LQTS

- Genetic polymorphisms (reduced repolarization reserve)

Other:

- Underlying heart disease, particularly heart failure, myocardial infarction, and left ventricular hypertrophy

- Recent conversion from atrial fibrillation [70]

- Female sex [71]
- Advanced age [66]

Most patients who have drug-induced TdP have one or more risk factors. In a literature review including 249 patients with TdP associated with noncardiac drugs, 97 percent had at least one risk factor, and 71 percent had at least two [72]. These included female sex in 71 percent, a history of heart disease in 41 percent, concurrent use of another QT-prolonging drug in 39 percent, hypokalemia in 28 percent, high drug dose in 19 percent, and a prior history of long QT syndrome in 18 percent.

The most frequent risk factor for drug-induced TdP is female sex [48,71,73,74]. In a literature review of 332 patients with TdP associated with cardiovascular drugs, 70 percent were females [71], similar to the 71 percent incidence associated with noncardiac drugs [72]. A female preponderance for symptomatic disease also has been noted in patients with congenital long QT syndrome [75].

Compared to males, females have a longer QTc and greater response to drugs that block IKr, potentiating the development of TdP [73]. This may be mediated by the effect of sex steroids on ion channel expression. Estrogen potentiates QT prolongation induced by bradycardia and the development of arrhythmia. In contrast, androgens shorten the QT interval and make it less responsive to drugs.

**Mutations in LQTS genes** — In some patients, drug-associated LQTS appears to represent a "forme fruste" of congenital LQTS in which a mutation or polymorphism in one of the LQTS genes is clinically inapparent until the patient is exposed to a particular drug or other predisposing factor. It has been suggested that there is a redundancy in repolarizing currents that has been called repolarization reserve [11]. This could explain why a given mutation might be associated with clinical disease only when another insult, such as a drug, hypokalemia, or hypomagnesemia, is superimposed. This topic is discussed in detail elsewhere. (See “Genetics of congenital and acquired long QT syndrome” section on ‘Mutations in acquired LQTS’.)

Summarized briefly, two observations illustrate the feasibility and magnitude of such a relationship:

- One report evaluated nine families with sporadic cases of LQTS; 15 of 46 family members (33 percent) who were felt to be unaffected based upon clinical criteria were gene carriers [76]. In such individuals, the LQTS mutations may produce an alteration in repolarizing currents that is insufficient to prolong the QT interval at rest. However, these silent gene carriers and their affected offspring might be at risk for unexpected TdP if exposed to drugs that can prolong the QT interval.

- Mutations affecting LQTS genes may be present in 5 percent of patients with drug-induced TdP and gene polymorphisms that might contribute to risk may be present in another 5 to 10 percent [34]. It has been estimated that one in 1000 to 3000 individuals may be a carrier of an LQTS mutation [34].

**Precautions when using QT prolonging drugs** — For patients who are treated with drugs that have been associated with LQTS (table 1) (and see www.qtdrugs.org), the following recommendations have been made [33]:

- Caution should be used when prescribing a drug that prolongs the QT interval in patients with one or more of the risk factors listed above. (See Risk factors' above.) Decisions regarding use of a QT prolonging drug should be based upon an individualized risk-benefit analysis. Alternative agents should be considered. Use of more than one QT prolonging drug should be avoided, if possible.

- A baseline electrocardiogram should be obtained prior to the administration of the drug.

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Electrocardiograms should also be obtained during the course of treatment to detect prolongation of the QT interval.

- Patients being treated with QT-prolonging drugs should be instructed to report promptly any new symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalemia, such as gastroenteritis or the initiation of diuretic therapy.

**OTHER CAUSES OF TdP**

**Hypokalemia, hypomagnesemia, and hypocalcemia** — Hypokalemia and hypomagnesemia can predispose to TdP. These disorders can occur together since hypomagnesemia directly causes hypokalemia. Hypocalcemia, alone or induced by hypomagnesemia, is a less common cause [77-79]. (See "Signs and symptoms of magnesium depletion", section on 'Hypokalemia' and "Signs and symptoms of magnesium depletion", section on 'Bone and calcium metabolism'.)

The risk for developing TdP in the presence of hypokalemia and/or hypomagnesemia is greatest in patients taking antiarrhythmic drugs [34,41,80-82]. This was illustrated in a report of 32 such patients [81]. Serum drug concentrations were in the therapeutic range in 22 of 26 patients in whom they were measured. However, 20 patients had, either alone or in combination, baseline prolongation of the QT interval, hypokalemia, or hypomagnesemia. In another series of 92 patients with drug-induced LQTS, 27 percent had hypokalemia or hypomagnesemia [34]. Similar findings were noted in a report of 24 patients with quinidine-induced LQTS: the serum quinidine concentration was well within the therapeutic range in one-half of patients and the serum potassium concentration was below 4.0 meq/L in 13 [41].

As noted above, virtually all of the drugs that produce LQTS act by blocking the IKr current mediated by the potassium channel encoded by the HERG gene [11-24,27]. The increase in risk with hypokalemia may be related to enhanced drug blockade of IKr [13]. The risk of hypokalemia itself may also be related to decreased IKr activity.

Further support for the importance of hypomagnesemia is the beneficial effect of magnesium administration in the acute therapy of TdP. (See 'Management' below.)

**Structural heart disease** — Heart failure and left ventricular hypertrophy are common risk factors for drug-induced TdP. Antiarrhythmic drugs and hypokalemia and/or hypomagnesemia associated with diuretic therapy may all contribute to proarrhythmia. It is not clear if there is an increased risk of LQTS or TdP with either type of heart disease alone.

Polymorphic VT is an uncommon arrhythmia following an acute myocardial infarction (MI) or ischemic episode. When it occurs, it typically is associated with a normal QT interval and with signs or symptoms of recurrent myocardial ischemia (waveform 3 and waveform 4) [83].

However, QTc prolongation may be common during the early phase of ischemia. In a series of 74 patients undergoing serial ECGs during angioplasty, all patients developed QT prolongation during balloon inflation [84]. In addition, some patients with acute myocardial infarction (8 of 434 consecutive patients in one series) develop progressive QT interval prolongation that is maximal at days three to 11 during the healing phase of the infarct [85]. By three months, the QT interval was normal in all but two patients treated with amiodarone. (See "Catecholaminergic polymorphic ventricular tachycardia and other polymorphic ventricular tachycardias with a normal QT interval", section on 'Polymorphic VT in coronary heart disease'.)

**Bradyarrhythmias** — As mentioned above, the likelihood of developing QT prolongation and TdP in patients taking antiarrhythmic drugs is increased by bradycardia due to reverse use dependency [13]. It is
less clear whether bradycardia alone causes TdP [86,87]. This issue was addressed in a report of 14 patients with complete atioventricular block, six of whom had a history of TdP [86]. The two groups did not differ with respect to the rate of the escape rhythm; however, the corrected QT interval was significantly longer in those who had experienced TdP (0.59 versus 0.48 sec). After pacemaker placement, the corrected QT interval was again significantly longer in those patients who had had TdP when the pacemaker was set at 60 beats per minute (0.55 versus 0.50 sec) or 50 beats per minute (0.70 versus 0.53 sec).

**Stroke** — QT prolongation is a common finding in patients with a stroke. In a review of 150 patients with acute stroke, QT prolongation was present in 45 percent of patients overall; and in 71 percent with subarachnoid hemorrhage, 64 percent with intraparenchymal hemorrhage, and 38 percent with ischemic stroke [88]. Occasional patients develop TdP, often in association with hypokalemia [89]. (See "Cardiac complications of stroke", section on 'QT prolongation'.)

**MONITORING** — The 2004 American Heart Association (AHA) practice standards for ECG monitoring in hospital settings include the following indications for QT interval monitoring [90]:

- Initiation of a drug known to cause TdP
- Overdose from potentially proarrhythmic agents
  - Since the types and amounts of drugs taken in an intentional overdose are frequently not known, monitoring of QT intervals may be prudent in all such cases [66].
- New-onset brady arrhythmias
- Severe hypokalemia or hypomagnesemia

The 2011 AHA/ACC scientific statement on prevention of TdP suggests a strategy of documenting the QTc interval before and at least every 8 to 12 hours after the initiation, increased dose, or overdose of QT prolonging drugs [66]. If QTc prolongation is observed, documentation of more frequent measurements is recommended.

The duration of QTc monitoring depends upon the duration of treatment with the QT prolonging drug and the drug half-life.

**DIAGNOSIS** — The QT interval typically is measured in lead II of a 12 lead ECG from the onset of the QRS complex to the point at which the T wave ends. The QT interval varies inversely with the heart rate; therefore, a correction for the heart rate (or the duration of the RR interval) must be made. A corrected QT interval (QTc) can be calculated from Bazett's formula:

\[ QTc = QT \text{ interval} \div \sqrt{RR \text{ interval (in sec)}} \]

The normal value usually cited for the QTc is ≤0.44 to 0.46 sec (440 to 460 msec) [1,91]. A QTc of more than 0.44 sec is considered prolonged in men; the normal range generally is extended to 0.45 to 0.46 sec in women [92]. The 2011 AHA/ACC scientific statement on prevention of torsade de pointes in hospital settings recommended that a QTc over the 99th percentile should be considered abnormally prolonged [66]. This corresponds to a QTc of >470 ms for men and >480 ms for women. A QTc >500 ms is considered highly abnormal for both men and women.

Among patients with possible acquired LQTS, there should be concern when there is more than a 25 percent increase in QTc from baseline; the risk of TdP does not vary predictably with the QTc but the risk
is greatest when the QTC is longer than 0.50 sec [91].

A limitation of Bazett's formula is that it produces overlong QTC values at faster heart rates (particularly over 85 bpm) [66]. A detailed discussion of which lead should be used for measurement, how to measure the interval, the method of correction for changes with heart rate, the limits of the normal range, and other factors used in diagnosis are discussed elsewhere. (See "Diagnosis of congenital long QT syndrome", section on 'QT interval'.)

**MANAGEMENT**

**General measures** — Patients presenting with a possible overdose of a QT-prolonging drug should be evaluated for risk of TdP.

The cornerstone of the management of patients with acquired LQTS is addressing the underlying cause by identifying and stopping any precipitating drug and aggressive correction of any metabolic abnormalities, such as hypokalemia or hypomagnesemia [93]. As noted above, correcting hypokalemia may be particularly important because a low serum potassium concentration enhances the degree of drug-induced inhibition of IKr, increasing the QT interval [13]. All drugs that prolong the QT interval (table 1) (and see www.qtdrugs.org) should be avoided because they appear to act by a common mechanism, inhibition of IKr [11-24].

Mild QT prolongation without TdP or syncope may be tolerated and monitored as an outpatient when it is associated with needed therapy with a drug known to cause it. Specific protocols for such management have not been established, but we suggest intermittent monitoring with ECGs and Holter recordings particularly at times of dose changes.

Patients with prolonged QT with syncope (without documented TdP) or ECG signs of instability (ventricular ectopy, T wave alternans, AV block or QRS widening) should be admitted for telemetry observation during withdrawal of the toxic agent (with immediate availability of an external defibrillator), and treatment of arrhythmias if indicated. In addition, admission and monitoring during drug withdrawal is suggested for patients with markedly prolonged QTC (>500 ms) or an increase in QTC of at least 60 ms compared with the predrug baseline value [66].

**Acute therapy of TdP** — Prompt nonsynchronized electric defibrillation is indicated in patients with hemodynamically unstable TdP [5,41]. However, in the conscious patient, a brief trial of medical therapy may be attempted prior to cardioversion. A number of acute therapies are available (table 3) [6,41,93]. The relative efficacy of these modalities was evaluated in a report of 24 patients with quinidine-induced LQTS, 20 of whom had TdP [41]. TdP was terminated in all nine patients who underwent ventricular pacing at rates of 100 to 120 beats/min, five of six treated with isoproterenol, and only seven of 14 receiving lidocaine.

Specific therapy of ventricular arrhythmia in acquired LQTS differs from that in congenital LQTS due in part to pathophysiologic differences between the two forms (table 3). As an example, a bradycardia usually is associated with TdP in acquired LQTS, whereas catecholamine surges trigger TdP in some types of congenital LQTS (figure 1).

- Intravenous magnesium sulfate is first-line therapy, being highly effective for both the treatment and prevention of recurrence of long QT-related ventricular ectopic beats or TdP [5,6,94]. The benefit occurs without shortening of the QT interval and is seen even in patients with normal serum magnesium concentrations at baseline.
The standard regimen consists of a 2 gram intravenous bolus of 50 percent magnesium sulfate over one to two minutes followed in 15 minutes by another such bolus if required [94]. Some patients also receive a continuous infusion at a rate of 3 to 20 mg/min. The bolus dose in children is 25 to 50 mg/kg; there are no published data on intravenous maintenance dosing in children.

- Temporary transvenous overdrive pacing (atrial or ventricular) generally is reserved for patients with long QT-related TdP who do not respond to intravenous magnesium [5,6]. Pacing at rates of about 100 beats per minute will decrease the dispersion of refractoriness and the development of early afterdepolarizations (EADs), and may shorten the surface QT interval, especially if there is an associated bradycardia. As noted above, many of the class IA and class III antiarrhythmic drugs that cause TdP have a property of "reverse use dependency," in which the QT interval decreases as the heart rate increases and lengthens as the heart rate slows [10]. These changes may be mediated in part by changes in the extracellular potassium concentration [13].

The efficacy of overdrive pacing was illustrated in a report of nine patients with life-threatening ventricular arrhythmias and drug-induced LQTS [95]. Acceleration of the heart rate produced immediate suppression of all arrhythmias, with a reduction in the QT interval from 0.65 to 0.50 sec. Similar findings were noted in another small series [96].

- Isoproterenol (initial dose 0.05 to 0.1 mcg/kg per min in children and 2 mcg/min in adults, then titrated to achieve a heart rate of 100 beats per minute) also can be used to increase the sinus rate and decrease the QT interval [5,6,97]. We favor placement of a temporary pacemaker in the treatment of most cases of TdP that do not respond to magnesium. However, isoproterenol can be used as a temporizing measure prior to pacing.

- Class IB antiarrhythmic drugs, such as lidocaine and phenytoin, shorten the action potential duration and, based upon small case series, may be effective in the acute management of TdP and ventricular fibrillation [41,98-101]. They appear to be less predictably effective than pacing or isoproterenol [6,41].

- Alkalization of the plasma, via the administration of sodium bicarbonate, is useful when TdP is due to quinidine [102]. Alkalization drives the reaction

\[ \text{Quin}^+ + \text{OH}^- \rightarrow \text{QuinOH} \]

to the right, thereby decreasing the availability of the active charged form of the drug and shortening the QT interval. (See "Enhanced elimination of poisons", section on 'Urinary alkalization'.)

- An intravenous infusion of potassium may be beneficial in patients with a normal baseline serum potassium concentration. The potential benefit of intravenous potassium was illustrated in a report of 20 normokalemic patients with QT prolongation due to quinidine or heart failure [103]. The administration of intravenous potassium (0.5 meq/kg to a maximum of 40 meq) raised the plasma potassium concentration by 0.7 meq/L, reversed QT prolongation and QT morphologic changes (U waves and bifid T waves), and decreased QT dispersion. It is uncertain, however, if this therapy is effective for preventing or reversing TdP.

**ACC/AHA/ESC Guidelines** — The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines for the management of
ventricular arrhythmias and the prevention of SCD addressed the management of TdP in the setting of acquired LQTS [93].

The guidelines stated that the weight of evidence supported the following options in patients with recurrent TdP:

- Intravenous magnesium
- Temporary pacing
- Isoproterenol

**Additional therapy** — In patients with eating disorders, nutritional rehabilitation will correct the QT prolongation over the longer term (three to 18 months) [104,105]. (See "Eating disorders: Treatment".)

A permanent pacemaker may be required in the occasional patient with a chronic bradyarrhythmia (due to sick sinus syndrome or atrioventricular block) who has bradycardia- or pause-dependent TdP (table 4). (See "Indications for permanent cardiac pacing".)

In addition to treating the underlying cause, a thorough history and ECG screening of immediate family members is recommended because of the occasional association with congenital LQTS. (See 'Mutations in LQTS genes' above and "Diagnosis of congenital long QT syndrome".)

Patients with acquired LQTS should be educated about the culprit drugs and other QT-prolonging drugs (including being provided with a list as available at www.qtdrugs.org) and potential drug-drug interactions [66].

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Long QT syndrome (The Basics)"

**SUMMARY AND RECOMMENDATIONS**

- Acquired LQTS usually results from drug therapy, hypokalemia, and/or hypomagnesemia (table 1). Some patients with acquired LQTS have an underlying "forme fruste" of congenital LQTS. (See 'Introduction' above.)

- Torsades de pointes (TdP) is a form of polymorphic ventricular tachycardia (VT) that occurs in the setting of acquired or congenital QT interval prolongation. TdP is usually short-lived and terminates spontaneously. However, most patients experience multiple episodes of the arrhythmia, and episodes can recur in rapid succession, potentially degenerating to ventricular fibrillation and sudden cardiac death. (See 'Torsades de pointes' above.)

- Acquired LQTS is commonly associated with bradycardia and pauses, in contrast to some forms of congenital LQTS (particularly types 1 and 2) (figure 1) in which arrhythmias often follow a sudden
**Acquired long QT syndrome**

- Adrenergic surge. (See 'Pathophysiology' above and "Clinical features of congenital long QT syndrome", section on "Triggers of arrhythmia".)

- Drugs that prolong the QT interval include antiarrhythmic drugs (classes Ia and III), certain nonselective antihistamines (e.g., terfenadine and astemizole), macrolide antibiotics, certain psychotropic medications, and certain gastric motility agents (e.g., cisapride) (see www.qtdrugs.org). (See 'Incidence with specific drugs' above.)

- Risk factors for drug-induced TdP include high concentrations (quinidine is an exception), concurrent use of other drugs that can prolong the QT interval or that slow drug metabolism due to inhibition of cytochrome P450 enzymes, concurrent intake of grapefruit juice, baseline QT prolongation or T wave lability, development of marked QT prolongation or T wave changes during therapy, bradycardia, electrolyte disturbances (particularly hypokalemia and hypomagnesemia), impaired hepatic and/or renal function, underlying heart disease, recent conversion from atrial fibrillation, and female sex. (See 'Risk factors' above.)

- Alternatives to QT prolonging drugs should be considered in patients with the above risk factors, particularly if the patient is already taking a QT prolonging drug. (See 'Precautions when using QT prolonging drugs' above.)

- Patients with prolonged QT with syncope (without documented TdP) or ECG signs of instability (ventricular ectopy, T wave alternans, AV block or QRS widening) should be admitted for telemetry observation during withdrawal of the toxic agent (with immediate availability of an external defibrillator), and treatment of arrhythmias if indicated. In addition, admission and monitoring during drug withdrawal is suggested for patients with markedly prolonged QTc (>500 ms) or an increase in QTc of at least 60 ms compared with the predrug baseline value [56].

- Prompt, nonsynchronized electric defibrillation is indicated in patients with hemodynamically unstable TdP.

- In the conscious patients with TdP, we suggest a brief trial of medical therapy (see 'Acute therapy of TdP' above):
  - Intravenous magnesium is first-line therapy, as it is highly effective for both treatment and prevention of recurrence of long QT-related ventricular ectopic beats of TdP. The benefit is seen even in patients with normal serum magnesium concentrations at baseline.
  - Temporary transvenous overdrive pacing (atrial or ventricular) at about 100 beats per minute is generally reserved for patients who do not respond to intravenous magnesium.
  - Isoproterenol (initial dose 0.05 to 0.1 mcg/kg per min in children and 2 mcg/min in adults, then titrated to achieve a heart rate of 100 beats per minute) can be used as a temporizing measure to achieve a heart rate of 100 beats per minute prior to pacing.

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**REFERENCES**


91. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003; 289:2120.


95. DiSegni E, Klein HO, David D, et al. Overdrive pacing in quinidine syncope and other long QT-


Prolonged QT interval

The corrected QT interval (QTc) is calculated by dividing the QT interval (0.60 seconds) by the square root of the RR interval (0.84 seconds). In this case, the QTc is 0.65 seconds.
Single lead electrocardiogram (ECG) showing torsades de pointes

This is an atypical, rapid, and bizarre form of ventricular tachycardia that is characterized by a continuously changing axis of polymorphic QRS morphologies.
The electrocardiographic rhythm strip shows torsades de pointes, a polymorphic ventricular tachycardia associated with QT prolongation. There is a short, preinitiating RR interval due to a ventricular couplet which is followed by a long, initiating cycle resulting from the compensatory pause after the couplet.
### Some reported causes and potentiators of the long QT syndrome*

<table>
<thead>
<tr>
<th><strong>Congenital</strong></th>
<th><strong>Acquired (continued)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jervell and Lange-Nielsen syndrome (including &quot;channelopathies&quot;)</td>
<td><strong>Antihistamines</strong></td>
</tr>
<tr>
<td>Romano-Ward syndrome</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Astemizole</td>
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<tr>
<td><strong>Acquired</strong></td>
<td><strong>Psychotropic drugs</strong></td>
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<tr>
<td><strong>Metabolic disorders</strong></td>
<td>Thioridazine</td>
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<tr>
<td>Hypokalemia</td>
<td>Phenothiazines</td>
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<tr>
<td>Hypomagnesemia</td>
<td>Tricyclic or tetracyclic antidepressants</td>
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<tr>
<td>Hypocalcemia</td>
<td>Haloperidol and other butyrophenones</td>
</tr>
<tr>
<td>Starvation</td>
<td><strong>Antineoplastic agents</strong></td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Crizotinib, dasatinib, eribulin, nilotinib, romidepsin, sorafenib, sunitinib, vandetanib, vemurafenib, vorinostat</td>
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<tr>
<td>Liquid protein diets</td>
<td><strong>Other drugs</strong></td>
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<tr>
<td>Hypothyroidism</td>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td><strong>Bradyarrhythmias</strong></td>
<td>Risperidone</td>
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<tr>
<td>Sinus node dysfunction</td>
<td>Opioids (methadone, oxycodone)</td>
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<tr>
<td>AV block - second or third degree</td>
<td>Vasodilators - prenylamine, bepridil, mibebradil</td>
</tr>
<tr>
<td><strong>Antiarrhythmic drugs</strong></td>
<td>Diuretics - via electrolyte changes (esp. hypokalemia or hypomagnesemia)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>5HT3-antagonists - ondansetron, granisetron, and dolasetron</td>
</tr>
<tr>
<td>Procainamide or N-acetylprocainamide</td>
<td>Motility drugs - cisapride, domperidone</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Droperidol - may be safe at the low doses used by anesthesiologists (0.625 to 1.25 mg)</td>
</tr>
<tr>
<td>Amiodarone and dronedarone</td>
<td>Ranolazine</td>
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<tr>
<td>Sotalol</td>
<td>HIV protease inhibitors</td>
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<tr>
<td>Dofetilide, ibutilide, azimilide, sematilide</td>
<td>Miscellaneous - organophosphate insecticides, proibucol, cocaine, terodiline, papaverine, certain Chinese herbs, chloral hydrate, arsenic trioxide, cesium chloride, levomethadyl</td>
</tr>
<tr>
<td><strong>Antimicrobial drugs</strong></td>
<td><strong>Other factors</strong></td>
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<tr>
<td>Erythromycin, clarithromycin, telithromycin, azithromycin</td>
<td>Myocardial ischemia or infarction, esp. with prominent T wave inversions</td>
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<tr>
<td>Pentamidine</td>
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<tr>
<td>Some azole antifungals - voriconazole, posaconazole</td>
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<tr>
<td>Some fluoroquinolones (eg, sparifloxacin, gatifloxacin, levofloxacin, moxifloxacin)</td>
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<tr>
<td>Other - spiramycin, chloroquine, halofantrine mefloquine</td>
<td>Intracranial disease</td>
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<td>HIV infection</td>
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<td>Hypothermia</td>
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<tr>
<td>Connective tissue diseases with anti-Ro/SSA antibodies</td>
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</table>

* The long and growing list of medications and other factors capable of prolonging the QT(U) represents an evolving area of clinical research. In some cases of long QT-U two or more factors may be involved. Additional clinical information is provided at the Arizona Center for Education and Research on Therapeutics (CERT) website: [http://www.azcert.org/medical-prcs/drug-lists/drug-lists.cfm](http://www.azcert.org/medical-prcs/drug-lists/drug-lists.cfm).
Triggers for cardiac events in long QT syndrome are related to genotype

In a study of 670 patients with a long QT syndrome (LQTS) and known genotype, the occurrence of a cardiac event provoked by a specific trigger (exercise, emotion, and sleep/rest without arousal) differed according to genotype. LQTS 1 patients experienced the majority of their events (62 percent) during exercise, while only 3 percent occurred during rest or sleep. These percentages were almost reversed among LQTS 2 and LQTS 3 patients, who were less likely to have events during exercise (13 percent) and more likely to have events during rest or sleep (29 and 39 percent, respectively).

### Inhibitors and inducers of cytochrome P450 3A4

<table>
<thead>
<tr>
<th><strong>Strong inhibitors</strong></th>
<th><strong>Moderate inhibitors</strong></th>
<th><strong>Strong inducers</strong></th>
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<tbody>
<tr>
<td>Atazanavir</td>
<td>Abiraterone</td>
<td>Aminoglutethimide</td>
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<tr>
<td>Boceprevir</td>
<td>Amiodarone</td>
<td>Armodafinil*</td>
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<tr>
<td>Chloramphenicol</td>
<td>Aprepitant</td>
<td>Bexarotene*</td>
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<tr>
<td>Clarithromycin</td>
<td>Bicalutamide</td>
<td>Bosentan</td>
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<tr>
<td>Cobicistat containing coformulations</td>
<td>Cimetidine</td>
<td>Carbamazepine</td>
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<tr>
<td>Conivaptan</td>
<td>Ciprofloxacin*</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Clotrimazole</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Crizotinib</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Cyclosporine</td>
<td>Etravirine</td>
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<td>Imatinib</td>
<td>Desipramine</td>
<td>Fosphenytoin</td>
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<tr>
<td>Indinavir</td>
<td>Diltiazem</td>
<td>Griseofulvin*</td>
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<tr>
<td>Isoniazid*</td>
<td>Danazol*</td>
<td>Mitotane*</td>
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<tr>
<td>Itraconazole</td>
<td>Dasatinib*</td>
<td>Modafinil*</td>
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<tr>
<td>Ketoconazole</td>
<td>Dronedarone</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Efavirenz</td>
<td>Nevirapine</td>
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<td>Nefazodone</td>
<td>Erythromycin</td>
<td>Oxcarbazepine</td>
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<td>Nelfinavir</td>
<td>Fluconazole</td>
<td>Pentobarbital</td>
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<td>Nicardipine</td>
<td>Fosaprepitant</td>
<td>Phenobarbital</td>
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<tr>
<td>Posaconazole</td>
<td>Grapefruit juice</td>
<td>Phenytoin</td>
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<tr>
<td>Ritonavir and ritonavir containing coformulations</td>
<td>Haloperidol</td>
<td>Primidone</td>
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<td>Saquinavir</td>
<td>Lapatinib</td>
<td>Rifabutin</td>
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<tr>
<td>Telaprevir</td>
<td>Metronidazole</td>
<td>Rifampin (rifampicin)</td>
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<td>Telithromycin</td>
<td>Miconazole</td>
<td>Rifapentine</td>
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<tr>
<td>Voriconazole</td>
<td>Mifepristone*</td>
<td>St. John's wort*</td>
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<td></td>
<td>Norfloxacin</td>
<td>Vemurafenib*</td>
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<td></td>
<td>Quinupristin-dalfopristin*</td>
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<td>Sertraline</td>
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<td>Sitaxsentan</td>
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<td>Tamoxifen*</td>
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<td>Tetracycline</td>
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<tr>
<td>Verapamil</td>
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<tr>
<td>Zafirlukast*</td>
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</table>

Degree of inhibition or induction may be altered by dose and method of administration. Specific drug interactions and management suggestions may be determined by using Lexi-Interact, the drug interactions program included with UpToDate.

* Less potent effect on CYP3A4 reported in some references.

Continuous rhythm strip revealing several episodes of nonsustained ventricular tachycardia (VT) occurring during an acute ischemic event. The QRS complexes are variable in morphology and RR intervals; thus, the VT is polymorphic. The QT interval is normal. This form of VT should be distinguished from torsade de pointes in which polymorphic VT is associated with QT interval prolongation.
ECG_2 showing polymorphic ventricular tachycardia in ischemia

Continuous rhythm strip showing an episode of very rapid polymorphic ventricular tachycardia which is often referred to as ventricular flutter. The QT interval is normal and the QRS complex morphology is highly variable. The patient had an underlying sinus tachycardia, suggesting increased sympathetic activity secondary to an ischemic event.
## Treatment of torsades de pointes due to long QT syndrome

### Acquired LQTS

**Pharmacologic**
- Magnesium sulfate
- Isoproterenol
- Lidocaine
- Phenytoin
- Sodium bicarbonate (for quinidine-related arrhythmia)

**Nonpharmacologic**
- Temporary pacing (atrial or ventricular)

### Congenital LQTS

**Pharmacologic**
- Beta blockers
- Mexiletine

**Nonpharmacologic**
- Permanent dual chamber pacemaker
- Left cardiac sympathetic denervation (cardiothoracic sympathectomy)
- Implantable cardioverter-defibrillator
ACC/AHA/HRS guideline summary: Indications for pacing to prevent tachycardia

Class I - There is evidence and/or general agreement that pacing should be used to prevent tachycardia in the following setting:
- Sustained pause-dependent ventricular tachycardia (VT), with or without QT prolongation. (Level of Evidence: C)

Class IIa - The weight of evidence or opinion is in favor of the usefulness of pacing to prevent tachycardia in the following setting:
- High-risk patients with congenital long QT syndrome. (Level of Evidence: C)

Class IIb - The weight of evidence or opinion is less well established for the usefulness of pacing to prevent tachycardia in the following setting:
- Prevention of symptomatic, drug-refractory, recurrent atrial fibrillation in patients with coexisting sinus node dysfunction. (Level of Evidence: B)

Class III - There is evidence and/or general agreement that pacing to prevent tachycardia is not useful in the following settings:
- Frequent or complex ventricular ectopic activity without sustained VT in the absence of the long QT syndrome. (Level of Evidence: C)
- Torsade de pointes VT due to reversible causes. (Level of Evidence: A)
