

## Guideline on drug-induced QT prolongation

Prolongation of the QT interval can lead to a life threatening ventricular arrhythmia known as torsades de pointes which can result in sudden cardiac death. There are a number of widely used drugs which are known to cause QT prolongation. The Medicines and Healthcare products Regulatory Agency (MHRA) has issued a number of warnings relating to drug-induced QT prolongation for some commonly used drugs – e.g. citalopram, escitalopram domperidone, ondansetron, hydroxyzine and quinine. Healthcare professionals require to be alert to the risk of drug induced QT prolongation and drug interactions. This guideline and associated flowchart has been developed to raise awareness and is relevant to all specialities and patients in primary and secondary care.

There are three mechanisms by which drugs can interact and increase the risk of QT prolongation:

- **Pharmacodynamic Interaction:** The concurrent use of more than one drug that prolongs the QT interval increases the risk of torsades de pointes and ventricular arrhythmia.
- **Pharmacokinetic Interaction:** Some drugs which do not prolong the QT interval themselves can increase the risk of QT prolongation by affecting the metabolism of drugs that do. Commonly used examples of this include antifungals which inhibit the CYP3A4 enzyme. Lists of drugs known to inhibit or induce liver enzymes can be found in Stockley's Drug Interactions: <https://www-medicinescomplete-com.knowledge.idm.oclc.org/#/browse/stockley>
- **Effects on Electrolytes:** Hypokalaemia and hypomagnesaemia can increase the risk of QT prolongation e.g. diuretics causing hypokalaemia can increase the risk of QT prolongation especially when given with QT prolonging drugs.

### What is a normal QT interval?

The QT interval varies with heart rate. A number of formulas are used to correct the QT interval for heart rate. Once corrected it is expressed as the QTc interval, which is reported on the ECG printout. The QTc is commonly normalised to a heart rate of 60bpm and may be inaccurate in patients with faster or slower heart rates.

**Normal QTc interval: <450 ms in males and <460 ms in females.**

### What is considered to be a prolonged QT interval?

The QTc interval is a surrogate marker of proarrhythmic risk and literature differs with regard to the QTc interval that would raise concern over development of arrhythmias. As a guide:

#### **Borderline QTc interval:**

**>450 ms but <500 ms in males**

**>460 ms but <500 ms in females**

Although literature differs, a QTc interval within these values is considered borderline prolonged. Consideration should be given to dose reduction of QT prolonging drugs or changing to an alternative non QT prolonging drug.

### **Prolonged QTc Interval: >500 ms in males and females**

A QTc interval >500 ms is clinically significant and likely to confer an increased risk of arrhythmia. Any drugs which prolong the QT interval should be reviewed immediately. Interpretation of the QT interval on an ECG is not always straightforward and the value noted on the computerised printout may not always be accurate. The following website gives some guidance on interpretation of the QT interval: <http://www.niccs.scot.nhs.uk>

### **What is considered a significant drug induced change in QTc interval?**

The degree by which a drug changes the QTc interval from baseline is also important. An increase in baseline QTc of less than 5 ms is not considered significant and this is the threshold for regulatory concern. For drugs that increase the QTc interval by less than 20 ms the data is inconclusive with regard to arrhythmic risk.

A change in baseline QTc of >20 ms should raise concern and a change of >60 ms should raise greater concern regarding the potential for arrhythmias. Experience in long QT syndrome indicates that for every 10 ms increase in QTc there is a 5-7% increase in the risk of arrhythmic events.

Drug induced QT prolongation is often dose related. For example, citalopram 20 mg daily has been shown to cause a mean change in baseline QTc of 7.5 ms; this increases to 16.7 ms with citalopram 60 mg daily. A drug induced increase in QTc interval should be assessed in conjunction with the overall QTc interval.

### **What are the risk factors for QT prolongation?**

In individual cases of torsades de pointes there are often multiple risk factors present. The main risk factors which should be considered are:

#### **Potentially Modifiable**

- Electrolyte Disturbances (in particular hypokalaemia, hypomagnesaemia and more rarely hypocalcaemia). Consider the risk of electrolyte disturbance if the patient has diarrhoea/vomiting
- Bradycardia
- Concomitant use of more than one drug that prolongs the QT interval

#### **Non-modifiable**

- Congenital Long QT Syndrome
- Cardiac Disease (of multiple origins, including congestive heart failure, ventricular hypertrophy, recent conversion from AF, myocardial infarction)
- Impaired hepatic/renal function (due to effects on drug metabolism)
- Thyroid Disease (more common with hypothyroidism and usually normalises with treatment)
- Female Sex
- Age over 65 years

## What medications can cause QT prolongation?

It is not possible to include a full list of all medicines known to increase the QT interval in this guideline.

A list of medications known to prolong the QT interval can be found in the credible meds website at <http://www.crediblemeds.org/>. This is an American website which categorises drugs based on their risk. It is recommended that you check the lists for drugs commonly used in your area of practice to familiarise yourself with the risks.

Alternatively, you can access a table from Stockley's Drug Interactions: <https://www-medicinescomplete-com.knowledge.idm.oclc.org/#/content/stockley/9.2Table>

Print versions of the BNF contain a table with a list of drugs that prolong the QT interval within Appendix 1, Interactions.

In addition to familiarising yourself with these sources, the BNF and Summary of Product Characteristics should be checked for individual drug contra-indications, cautions and interactions.

Some of the more commonly encountered medicines known to prolong the QT interval are listed in the table below. These medicines are either listed by CredibleMeds® as known to have a high risk of torsades de pointes, are described as high risk in Stockley's Drug interactions, are included in the BNF table or have had MHRA alerts to highlight risk of QT prolongation.

<b>QT Prolonging Medicines</b>	
<b>Class</b>	<b>Medicines</b>
<b>Antimicrobials</b>	Azithromycin Ciprofloxacin Clarithromycin Erythromycin Fluconazole Levofloxacin Moxifloxacin
<b>Antidepressants</b>	Many antidepressants have been associated with QT prolongation in overdose. For this reason they should be used with caution. The following are considered high risk at therapeutic doses: Citalopram Escitalopram Tricyclic antidepressants
<b>Antipsychotics</b>	Many antipsychotics have a risk of QT prolongation, and should be used with caution in patients with other risk factors. The following are considered high risk: Chlorpromazine Haloperidol Pimozide Sulpiride
<b>Antiarrhythmics</b>	Amiodarone Disopyramide Dronedarone Flecainide Sotalol

<b>Antiemetics</b>	Domperidone Ondansetron
<b>Others</b>	Anagrelide Hydroxyzine Methadone Quinine Tolterodine Lithium Hydroxychloroquine / Chloroquine Protein kinase inhibitors and some other oncology drugs – seek specialist advice if unsure Some antimalarials Some antiretrovirals* *Lopinavir/Ritonavir: although not known to prolong QT interval, particular caution is needed when co-administered with medications that prolong the QT interval due to strong effect on CYP3A enzymes

### **What can be done to minimise the risks of drug induced QT prolongation?**

The risk of torsades de pointes depends on patient factors and current medication. A safe drug in one patient may be potentially harmful in another. The risks and benefits must be determined on a case by case basis.

As general guidance:

- Consider the risk of QT prolongation when starting a new medicine (if unsure of medicine related risk contact pharmacy for advice).
- Assess patient's risk factors for QT prolongation.
- Avoid QT prolonging drugs in patients with congenital long QT syndrome.
- Correct any modifiable risk factors such as electrolyte disturbance.
- **Where a patient has risk factors and/or is prescribed an interacting medicine, the first line option is to change to an alternative drug that is not known to prolong the QT interval wherever possible.**
- If the decision is made to concurrently prescribe two drugs that are known to prolong the QT interval this should be clearly documented in the medical notes. If the combination is contra-indicated specialist advice must be sought.

### **When would ECG monitoring be recommended?**

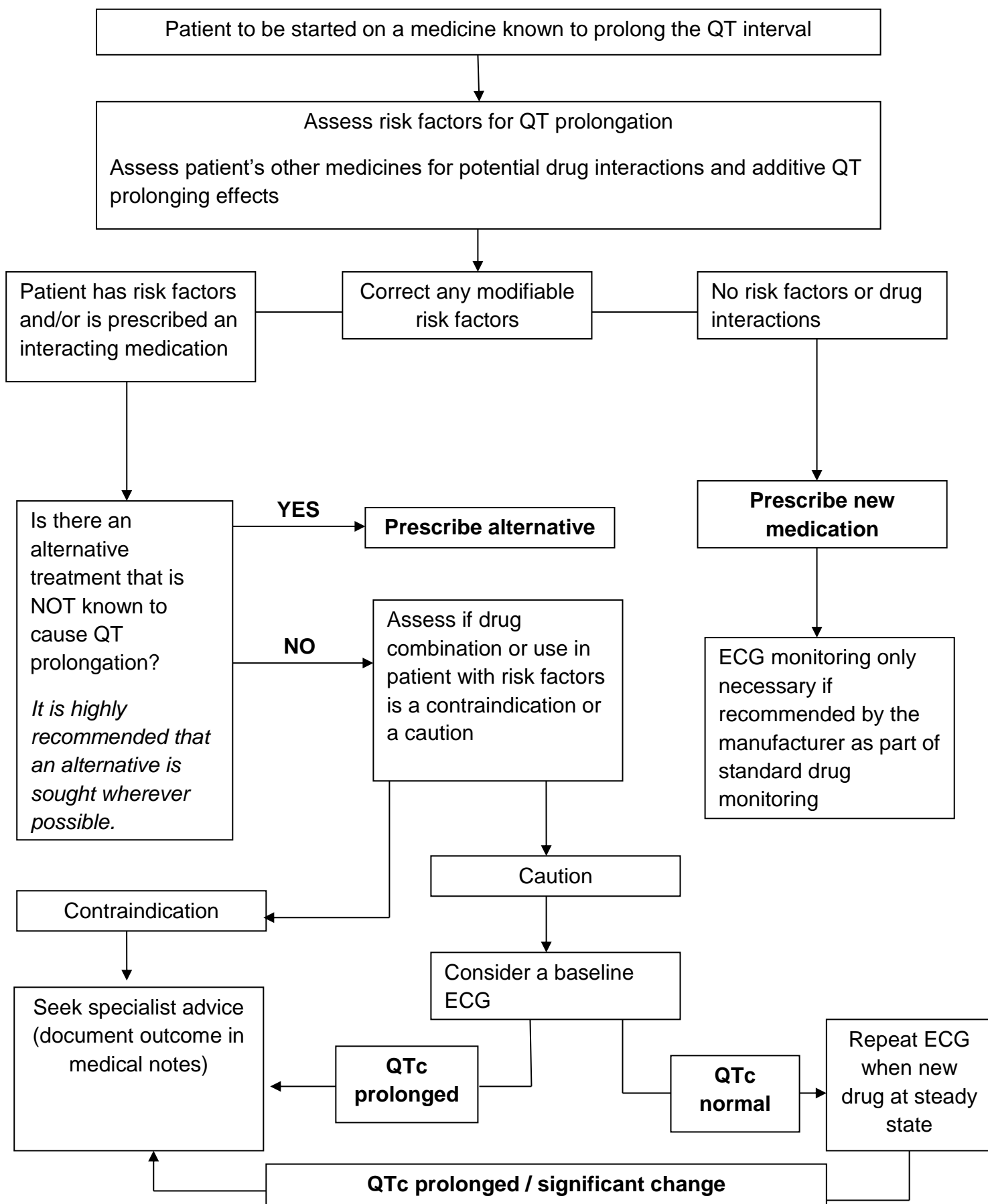
The following advice is aimed at the non-specialist. Specialist areas using medicines known to prolong the QT interval may have local guidelines to follow.

It is not practical to recommend an ECG every time a QT prolonging medicine is prescribed, particularly in primary care. The decision should be made on a case by case basis taking into account any additional risk factors the patient has. The following could be considered as a guide:

- Consider carrying out a baseline ECG prior to starting a QT prolonging drug in patients with risk factors then repeat when the medicine reaches steady state. Inform the patient of potential adverse effects to be aware of.
- If there is no alternative to using two drugs in combination that are known to prolong the QT interval, especially in patients with additional risk factors, carry out an ECG at baseline and then repeat when the new medicine is likely to reach steady state.

- If long term use of two medicines that can prolong the QT interval is deemed necessary the patient should be followed up and monitored via specialist clinic.
- Any patient on a QT prolonging drug who reports symptoms such as palpitations, light-headedness and dizziness should be referred for investigation and have their medication reviewed.
- If a prolonged QT interval is detected on an ECG during hospital admission, ensure communication with the GP on discharge including any medication changes.

## DRUG INDUCED QT PROLONGATION FLOWCHART



Adapted with kind permission from NHS Greater Glasgow and Clyde April 2020