**Drugs and life-threatening ventricular arrhythmia risk: results from the DARE study cohort**

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**Short title:** Drugs causing proarrhythmia

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**ABSTRACT**

**Objectives**

To establish a unique sample of proarrhythmia cases, determine the characteristics of cases and estimate the contribution of individual drugs to the incidence of proarrhythmia within these cases.

**Setting**

Suspected proarrhythmia cases were referred by cardiologists across England between 2003 and 2011. Information on demography, symptoms, prior medical and drug histories and data from hospital notes were collected.

**Participants**

Two expert cardiologists reviewed data for 293 referred cases: 130 were included. Inclusion criteria were: new onset or exacerbation of pre-existing ventricular arrhythmias; QTc >500ms; QTc >450ms (males) or >470ms (females) with cardiac syncope; all secondary to drug administration. Exclusion criteria were: acute ischaemia and ischaemic polymorphic ventricular tachycardia at presentation; structural heart disease; consent withdrawn or deceased prior to study. Descriptive analysis of Caucasian cases (95% of included cases, N=124) and culpable drug exposures was performed.

**Results**

Of the 124 Caucasian cases: 95 (77%) were QTc interval prolongation-related; mean age was 62 years [SD 15]; and 63% were female. Cardiovascular comorbidities included hypertension (53%) and patient-reported ‘heart rhythm problems’ (73%). Family history of sudden death (36%) and hypokalaemia at presentation (27%) were common. 165 culpable drug exposures were reported, including antiarrhythmics (42%) of which amiodarone and flecainide were most common. Sotalol, a beta-blocking agent with antiarrhythmic activity, was also common (15%). 26% reported multiple drugs, of which 84% reported at least one CYP P450 inhibitor. Potential pharmacodynamics interactions identified were mainly QT prolongation (59%).

**Conclusions**

Antiarrhythmics, non-cardiac drugs and drug combinations were found to be culpable in a large cohort of 124 clinically-validated proarrhythmia cases. Potential clinical factors that may warn the prescriber of potential proarrhythmia include: older females; underlying cardiovascular comorbidity; family history of sudden death; and hypokalaemia.

**KEY WORDS**

Proarrhythmia; epidemiology; QT interval prolongation

**STRENGTHS AND LIMITATIONS OF THE STUDY**

**Strengths**

* The DARE study has allowed the development of a cohort of cases of proarrhythmia
* These cases have provided crucial safety information, as well as underlying clinical and genetic data

**Limitations**

* Only patients who did not die as a result of the proarrhythmia could be included
* Referral of cases by cardiologists only may have led to the underestimation of the prevalence of drug-induced arrhythmia from non-cardiac drugs
* The analysis of ethnicity and differences in risk of QT prolongation could not be investigated

**INTRODUCTION**

Drug-induced arrhythmia, or proarrhythmia, is the induction or exacerbation of cardiac arrhythmia associated with administration of a drug. The majority of drug-induced arrhythmic events relate to marked prolongation of the QT interval of the electrocardiogram which can lead to the distinctive polymorphic ventricular tachycardia, ‘Torsades de Pointes’ (TdP) which in turn may lead to ventricular fibrillation (VF) and sudden death (1). This is also known as the acquired long QT syndrome (aLQTS). Occasionally polymorphic and monomorphic ventricular tachycardia (VT) without QT prolongation can occur (2, 3). In addition to drugs, other causes of aLQTS include endocrine disorders (4), cirrhosis (5), Human Immunodeficiency Virus (HIV) and acquired immune deficiency syndrome (AIDS) (6), inflammation and immunity (7), autoimmune disease (8), structural heart disease (9), electrolyte imbalances (10) and eating disorders (11).

Drug-induced arrhythmia is associated with the use of cardiovascular agents (particularly class III antiarrhythmic drugs) and also with many non-cardiovascular indicated drugs within different therapeutic categories including antihistamines, antipsychotics and antimicrobials; an up-to-date list is maintained on the CredibleMeds® register (Azcert Inc., <https://crediblemeds.org/>). Currently, there is substantial evidence to support a clear association between over 50 different drugs and risk of TdP, even when taken according to the terms of the marketing authorisation, with a number of these being withdrawn from the market (12-14). Mechanistic proposals for clinical features such as electrolyte imbalance include block of the rapid form of the delayed rectifier potassium current (IKr) in cardiomyocytes (15-17). Genetic factors have also been identified. These include single nucleotide polymorphisms (SNP) in the *NOS1AP* gene encoding the nitric oxide synthase 1 adaptor protein (18); and mutations in potassium channel genes *KCNH2, KCNQ1, KCNE1* and *KCNE2* and/or the sodium channel gene *SCN5A* (19, 20). Such mutations are also recognised to cause congenital long QT syndrome (cLQTS) (21). Other notable risk factors include female sex, bradycardia, recent cardioversion, pre-existing electrolyte disturbance, elevated plasma concentrations and/or rapid infusion of QT prolonging drugs and digitalis toxicity (22-24).

Following the removal of several QT prolonging drugs because of associated sudden deaths (25-28), risk minimisation strategies were introduced to mitigate the arrhythmic risk posed by drugs, including clinical studies to assess the proarrythmic potential for a new drug within the pre-marketing development programme (29). However it has been recognised that there remain limitations in the conduct of clinical studies designed to evaluate a drug’s potential for QT prolongation and applicability of results to vulnerable patients (30). Because of the unpredictable nature of the condition, the Drug-induced Arrhythmia Risk Evaluation (DARE) study aimed to improve the understanding of the epidemiology of proarrhythmia by establishing a cohort of cases of drug-induced arrhythmia reported throughout England, to characterise typical patients with proarrhythmia and to describe the drugs found to be culpable in these cases of proarrhythmia. This manuscript is a per protocol descriptive analysis of risk factors for the condition and the contribution of individual drugs to the risk of drug-induced arrhythmic events.

**METHODS**

## **Study design and setting**

Cardiologists across England were notified of the study by the British Pacing and Electrophysiology Group (BPEG) and the British Cardiac Society (BCS) and asked to recruit patients. Study awareness and participation was further promoted by project presentation and local interaction across the country. Cases of suspected proarrhythmia were referred by cardiologists in England between March 2003 and July 2011. All consenting cases attended a face-to-face interview with a regional study nurse (North, South or Midlands regions) between May 2005 and August 2011.

## **Participants**

Cases of proarrhythmia were included if they had one or more of the following criteria, all diagnosed as secondary to therapeutic drug administration or overdose: documented TdP, VF or VT (polymorphic or monomorphic, not associated with QT prolongation); exacerbation of pre-existing non-sustained arrhythmias to sustained; severe prolongation of the QTc interval corrected using Bazett’s formula (>500ms) without symptoms; or moderate prolongation of the QTc interval (≥ 450ms in males or ≥470ms in females) with a clinical history of cardiac syncope.

All cases were reviewed by at least two experienced cardiologists, using hospital notes and interview questionnaire information, to ensure appropriate inclusion of cases. Patients with acute ischaemia, ischaemic polymorphic VT and structural heart disease (using symptoms, previous history of ischaemia and associated therapy, risk factors or ECG, stress test and coronary angiography results) were excluded. Case presentation (asymptomatic, syncope, VT, VF and/or TdP) and aetiology (QT prolongation associated and non-QT prolongation associated) were ascertained. Drugs received by the patient were adjudicated for culpability in contributing to proarrhythmia according to the clinical data, timing of medication and the presenting event that prompted referral. Prior reports of association with proarrhythmia were also taken into account although drugs thought to contribute to causation but without such data were not excluded.

No sample size calculation could be performed for the study as, at the time of study initiation, the natural history, relative risk and potential risk factors of proarrhythmia were largely unknown.

## **Variables**

A pro-forma questionnaire obtained patients’ self-reported information on age, gender, ethnicity, weight, height, smoking status, alcohol consumption, symptoms before, during and after the event (including ‘blackout’, ‘near blackout’, ‘dizziness/light-headedness’ and ‘palpitations’), medication taken before, during and after the event (including prescription, over-the-counter/herbal and recreational), any past medical and cardiovascular history (including angina, myocardial infarction, ‘heart failure’, ‘heart valve problem’, ‘heart rhythm problem’, ‘high blood pressure’, hypokalaemia, hypothyroidism, diabetes mellitus, ‘stroke’, transient ischaemic attack, ‘liver problem’, ‘kidney problem’) and family medical history (including ‘sudden death’ and ‘unexplained blackout’). History of proarrhythmic events was validated using each patient’s hospital notes and an ECG taken at the time of the interview. Patient hospital notes, where available, were also used to validate drug history (including the drug(s) considered to be related to the proarrhythmic event), previous medical and cardiovascular history for all cases.

Culpable drugs were mapped to the Anatomical Therapeutic Chemical (ATC) classification system. The drugs were then classified according to the CredibleMeds® register risk of causing QT prolongation and/or TdP into the following groups: known risk, possible risk, conditional risk and no known risk. Drugs are classified as having: known risk when there is substantial evidence for QT interval prolongation and TdP risk when used according to the label; possible risk when there is substantial evidence for QT interval prolongation but insufficient evidence of TdP risk when used according to the label; conditional risk when there is substantial evidence for QT interval prolongation and TdP risk but only under specific conditions (e.g. overdose, interaction with another drug). Drugs were also classified according to cytochrome P450 activity (inhibitors and inducers) and potential pharmacodynamics interactions were identified using the Drug Interaction Checker (Medscape). Potential pharmacodynamics interactions were classified into one of the following groups: QTc prolongation; cardiotoxic (non QTc prolongation related but other cardiac effect likely, e.g. bradycardia or other dysrhythmia); conditional (cardiac effect unclear but drug interaction has an impact on a proarrhythmic risk factor, e.g. potassium levels); other (non-cardiovascular) or no drug interaction.

## **Statistical methods**

Statistical analysis involved descriptive statistics, including measures of central tendency and dispersion for continuous variables (mean, standard deviation, median, range, and percentiles) and frequencies with proportions for categorical variables. Results were also stratified according to type of arrhythmia (QT prolongation associated or and non-QT prolongation associated). All statistical analyses were performed using STATA v12 (Special Edition, Stata Corporation, USA). Radar plots were also constructed in order to characterise cases and estimate the contribution of individual drugs to risk of proarrhythmia. Missing information relating to patients was described using a ‘not known’ category.

**RESULTS**

## **Case characteristics**

The final overall cohort consisted of 130 cases (Figure 1) which were referred from a total of 98 consultant cardiologists across England (Figure 2). As the majority of cases were Caucasian (n = 124, 95.4%) the analysis was performed on these individuals only. Characteristics of the final cohort of Caucasian cases are shown in Table 1. Cases were 62.9% female with a median age at interview of 66 years (IQR 52-73 years). All cases were adults (≥18 years). Around a third (35.5%) had a family history of sudden death. The types of arrhythmia reported in cases is shown in Table 1. The majority of cases reported TdP, VF or cardiac arrest with QT prolongation (n = 79, 63.7%); of which 56 (45.2%) presented with TdP, 13 (10.5%) presented with VF and 10 (8.1%) presented with TdP and VF. However, 23% (n = 28) of cases involved VT or VF not related to QT prolongation. Median (SD) QTc values were 578 (69) ms in QT prolongation associated cases and 466.7 (40) ms in non-QT prolongation associated cases.

## **Culpable drugs**

A total of 165 patient drug exposures to 42 drugs deemed culpable were identified (Table 2, two drugs were unspecified). The most frequent associated drug class was the anti-arrhythmics, with 70 drug exposures (42.4% of drug exposures) in 67 (54.0%) patients. Amiodarone (n = 40; 24.2% of drug exposures; 32.3% of patients), flecainide (n = 23; 13.9% of drug exposures; 18.6% of patients) and sotalol, a beta-blocker with Class III properties, (n = 25; 15.2% of drug exposures; 20.2% of patients) were the most frequently reported single drug causes and known to carry a risk of QTc prolongation and/or TdP. Antibiotics (e.g. erythromycin; n = 5, 3.0% of drug exposures, 4.0% of patients) and anti-depressants (e.g. citalopram; n = 7, 4.2% of drug exposures, 5.7% of patients) were also implicated.

Of the 42 culpable drugs: 14 (33.3%) drugs carried a known risk (120 [72.7%] drug exposures); 8 (19.0%) carried a conditional risk (16 [9.7%] drug exposures); 6 (14.3%) carried a possible risk (7 [4.2%] drug exposures); 1 (2.4%) carried a risk in individuals with cLQTS; and 13 (31.0%) carried no known risk of QTc prolongation and/or TdP (18 [10.9%] drug exposures). The level of risk could not be established for 2 drugs.

Of the 13 culpable drugs carrying no known risk of QTc prolongation and/or TdP; two are known to contribute to bradycardia (timolol and digoxin), two are ‘not classified’ according to CredibleMeds based on the evidence available (cetirizine and verapamil) and one remains under active review (lofexidine).

Multiple drug combinations (Table 3) were reported in 32 (25.8%) patients. Specifically, 27 (21.8%) patients reported two drugs, 2 (1.6%) patients reported three drugs, 2 (1.6%) patients reported four drugs and 1 (0.8%) patients reported five drugs. Two patients had unspecified drug combinations. Of the patients reporting more than one drug, 84.4% (27/32) reported using at least one cytochrome P450 inhibitor, with 6 (18.8%) using two or more in combination. A single patient reported using a CYP inducer. Potential pharmacodynamics interactions within patients reporting more than one drug, according to the Medscape Drug Interaction Checker, were QTc prolongation (19/32, 59.4%), cardiotoxic (3/32, 9.4%), conditional (1/32, 3.1%) and other (non-cardiovascular; 2/32, 3.6%) interactions. Seven patients (21.9%) reported a drug combination without a potential drug interaction.

## **Types of Arrhythmia**

Types of proarrhythmia identified within this study included QT prolongation-related (n = 95, 76.6%) and non QT prolongation-related (n = 29, 23.4%), the latter more typically associated with QRS prolongation. (Table 2). Stratification according to proarrhythmia type demonstrated few differences between the characteristics of QT prolongation-related and non QT prolongation-related cases of proarrhythmia, with similar frequency of past medical conditions within both types (Figure 3). Similarly drugs deemed culpable in cases of proarrhythmia were similar between these types, except for flecainide, which was more commonly implicated with non QT prolongation-related compared with QT prolongation-related (Figure 4).

**DISCUSSION**

The DARE study established a cohort of 130 cases of clinically-validated drug-induced proarrhythmia referred from across England. To our knowledge this is the largest single study describing a cohort of cases of drug-induced arrhythmia. This information can be used in conjunction with other methods for evaluating the risk of drug-induced arrhythmias; such as spontaneous reports, healthcare databases and active surveillance studies. An analysis of 124 Caucasian cases was undertaken. These Caucasian cases were predominantly female (62.9%) and middle aged or elderly (median age at interview of 66 years [IQR 52-73 years]). The majority reported significant past cardiac comorbidity including heart rhythm problems (72.6%), high blood pressure (53.2%), heart valve problems (27.4%), angina (21.0%) and myocardial infarction (21.8%). This is consistent with data that demonstrate arrhythmia or heart failure to be a risk for proarrhythmia (31). Over a third of cases also had an associated family history of sudden death, supporting the potential genetic risk for drug-induced arrhythmia (21). Additionally, over a quarter of cases presented with hypokalaemia (26.6%). Hypokalaemia, is associated with QT interval prolongation due to increased competitive blockade of IKr which causes loss of function of the hERG (human Ether-a-go-go Related Gene) channel (16).

Risk factors for proarrhythmia have been studied before. For example, one study demonstrated hypokalaemia, myocardial infarction, sepsis and heart failure to be risk factors for QT prolongation in both drug-induced and non-drug-induced hospitalised cases (32). Furthermore, a study of 21 patients with drug-induced QT prolongation from a Greek Hospital found hypertension, female gender, paroxysmal atrial tachyarrhythmias and old age (>60 years) to be common characteristics of patients presenting with the condition (33). Finally, a study of a group of methadone users in Switzerland demonstrated greater risk of QT prolongation with hypokalaemia, higher methadone dose, altered liver function and use of P450 cytochrome inhibitors (34). A study of psychiatric patients with drug-induced LQTS showed hypokalaemia, abnormal T wave as well as hepatitis C and human immunodeficiency virus infection to increase the risk of LQTS in this population (35).

In our study amiodarone, sotalol and flecainide were the most common culpable drugs as was the anti-arrhythmic drug group as a whole (42.2% of drug exposures). Their high prevalence may be due to the relative high potency of cardiac current blockade and/or reflect that cardiologists were the main referral source of cases. For example clinical trials of patients with ventricular and supraventricular arrhythmias treated with sotalol have shown a 4.3% prevalence of proarrhythmia (36). Whilst class Ia, Ic and III antiarrhythmics carry a known risk of QT prolongation and/or TdP and can be potent IKr blockers, amiodarone is often thought of as a rare cause of TdP (37). Its importance in our cohort may be due to its relatively frequent use as an antiarrhythmic agent and/or that those most vulnerable to aLQTS (i.e. elderly females with cardiac comorbidity) are more likely to receive amiodarone than other antiarrhythmics due to its perceived lower proarrhythmic risk. This is therefore an important warning to clinicians. Proarrhythmia unrelated to QT prolongation was most commonly observed in users of flecainide, recognised to result from conduction slowing causing QRS duration prolongation (38). Amiodarone was also frequently reported to be associated with LQTS and TdP in a recent active surveillance study of 58 cases in Germany; a study which showed similar results to DARE, including the identification of hypokalaemia as a risk factor for LQTS and TdP (39).

Nearly three-quarters of the culpable drug exposures were caused by drugs with known risk of QT prolongation and/or TdP, including antibiotics and antidepressants. However, 13 (31.0%) different drugs were diagnosed as culpable in proarrhythmia but not recognised as having such a risk according to the CredibleMeds register. Two are known to contribute to bradycardia (a risk for proarrhythmia), two are ‘not classified’ according to CredibleMeds based on the evidence available and one remains under active review (lofexidine). Drug combinations were also culpable in a quarter of cases, with up to five drugs being reported in combination. Of these drug combinations by far the majority, 84.4% (27/32), included at least one cytochrome P450 inhibitor. Drug combinations of antipsychotics and antidepressants have also previously been shown to increase the risk of QT interval prolongation when compared with antipsychotics alone (40). Concurrent use of more than one QT-prolonging drug or concurrent use with a drug that alters the pharmacokinetic profile of the drug is an important risk factor for adverse outcomes. On the other hand, other studies have shown no increased risk of QT interval prolongation with the use of multiple QT-prolonging drug combinations compared with single drugs (32). Furthermore, drugs with no known risk of QTc prolongation when used alone, may result in prolongation of the QTc interval when used in combination. For example, ceftriaxone and lansoprazole were identified as having a risk of QTc prolongation when used together using electronic healthcare records and *in vitro* methodology (41). Drug interactions were also reported to represent a high proportion of cases of drug-induced TdP within a Belgium study using the EudraVigilance database (18 of 31 cases) (42).

Limitations of the DARE study include the inability to enrol patients who may have suffered from sudden death as a result of drug-induced arrhythmia; for ethical reasons only live patients could be included. Furthermore, as all referrals came from cardiologists, this may have resulted in selection bias and underestimation of the prevalence of drug-induced arrhythmia from non-cardiac drugs. The level of underestimation due to sudden death or cardiologist referral is difficult to quantify. Determining the cause of death in patients with sudden cardiac death is challenging, with ion channelopathies, potentially accounting for 40% of cases of Sudden Arrhythmic Death Syndrome, being undetectable after a patient has died (43). A comparison with spontaneous reports of drug-induced arrhythmia might provide information on the level of underestimation of the prevalence of drug-induced arrhythmia from non-cardiac drugs; however, underreporting of severe adverse drug reactions is known to be high, at approximately 80% (44). In addition, patient answers to questionnaires may have been subject to recall bias and some of the patient information could not be validated from patient records. Finally, differences in ethnicity could not be investigated in this group as there were too few cases of non-Caucasian ethnic origin. Ethnic differences have been shown to affect the risk of QT prolongation due to polymorphisms in cardiac ion channels (45). With a larger number of cases, ethnicity differences could be further investigated. It would also be desirable to estimate the incidence of proarrhythmia within the UK population, as has been done for a similar study (39). Future work might also involve an investigation of specific drug types and how exposure duration and patterns of usage might affect the risk of proarrhythmias.

**Conclusions**

Increased awareness in the past decade of the public health risk of QT prolonging drugs has resulted in the regulatory authorities producing guidelines for studying the potential for QT prolongation in premarketing development and the adoption of risk-minimisation measures (29). However, due to rarity and diagnostic difficulties, the lack of reported TdP cases in pre-marketing or post-marketing safety monitoring is a challenge for drug safety (46). To date, linked epidemiological and pharmacogenetic data on proarrhythmic events has been lacking. As such, the DARE study has allowed the development of a cohort of cases which provide crucial safety information, as well as underlying clinical and genetic data (18, 47, 48). DARE have provided information that confirms risk factors for proarrhythmia, including patient co-morbidities and use of drugs with known QTc prolongation risk. However, the study has also identified higher frequency of amiodarone as well as reports of drugs with no known QTc prolongation risk.

Caution is necessary when prescribing class I and III anti-arrhythmic drugs. This includes amiodarone given its frequent use in clinical practice. The prescriber needs to be aware of a patient’s concomitant medications and co-morbidities, especially middle age to elderly females with cardiovascular disease and/or a family history of sudden death, as well as the likelihood of hypokalaemia. Furthermore prescribers must be aware of the contribution of non-cardiac drugs to the burden of drug-induced arrhythmias (49), with approximately 3% of prescriptions in the UK representing non-cardiac drugs with warnings for arrhythmic potential (50). Our findings reinforce the need for safer prescribing of proarrhythmic drugs in clinical practice.

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**CONTRIBUTORS**

AJC, SAWS ERB and DL designed the study. VM was responsible for data acquisition. ALC, DL and ERB performed the analyses. ALC, DL, VM, ERB, AJC, and SAWS interpreted the findings. ALC, VM, ERB and DL wrote the first draft of the manuscript and revised subsequent versions. The other authors provided input, expertise, and critical review of the paper. All authors read and approved the final version of the paper. AJC and SAWS are the guarantors.

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**COMPETING INTERESTS**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: ERB was supported by grants from the international Serious Adverse Events Consortium during the conduct of the study. SAWS reports personal fees from ICON, Shire Pharmaceuticals, ONO Pharmaceuticals, Intermune Pharma and IPSEN outside of the submitted work. AJC reports personal fees from Mitsubishi, Laguna, Bayer, Biotronik, Richmond Pharmacology, Boehringer Ingelheim, Daiichi, Menarini, Novartis, St. Jude Medical, Bristol Myers Squibb, Pfizer, Medtronic, Thrombosis Research Institute, Servier, Boston Scientific, Eli Lilly and Company and organisational (non-commercial) fees from the European Heart Rhythm Association outside the submitted work.

**ETHICAL APPROVAL**

Ethical approval was gained from the London Multicentre Research Ethics Committee (MREC), reference number MREC/02/2/73.

**DATA SHARING**

Additional data available on request by emailing abigail.coughtrie@dsru.org.

**TRANSPARENCY STATEMENT**

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**EXCLUSIVE LICENCE STATEMENT**

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**FIGURES**

**Figure 1.** Referrals and cohort accrual

**Figure 2.** Geographic distribution of consultant cardiologists referring proarrhythmia cases

**Figure 3.** Characteristics of QTp and non-QTp related cases of proarrhythmia

**Figure 4.** Drugs (ATC codes) culpable in cases of proarrhythmia

**TABLES**

**Table 1.** Characteristics of cases (N = 124)

|  |  |
| --- | --- |
| **Characteristics** | **n (% of cases)** |
| **Gender** |  |
| Female | 78 (62.9) |
| Male | 46 (37.10) |
| **Age at interview (years)** |  |
| 10-19 | 2 (1.6) |
| 20-29 | 2 (1.6) |
| 30-39 | 7 (5.7) |
| 40-49 | 15 (12.1) |
| 50-59 | 20 (16.1) |
| 60-69 | 33(26.6) |
| 70-79 | 37 (29.8) |
| 80-89 | 8 (6.5) |
| Median (IQR) | 66 (52-73) |
| **Smoking Status** |  |
| Current | 13 (10.5) |
| Ex-smoker | 58 (46.8) |
| Never smoked | 51 (41.1) |
| Not known | 2 (1.6) |
| **Alcohol Use** |  |
| Yes | 92 (74.2) |
| No | 32 (25.8) |
| **Body Mass Index (kg/m2)** |  |
| <18.5 (underweight) | 5 (4.0) |
| 18.5-24.9 (normal) | 55 (44.4) |
| 25-29.9 (overweight) | 31 (25.0) |
| ≥30 (obese) | 33 (26.6) |
| **Family history** |  |
| Unexplained syncope | 17 (13.7) |
| Sudden Death | 44 (35.5) |
| **Prior medical history\*** |  |
| High blood pressure | 66 (53.2) |
| Hypokalemia | 33 (26.6) |
| Hypothyroidism | 22 (17.7) |
| Angina | 26 (21.0) |
| Myocardial infarction | 27 (21.8) |
| Heart failure | 17 (13.7) |
| Cardiomegaly | 21 (16.9) |
| Heart value problem | 34 (27.4) |
| Heart rhythm problem | 90 (72.6) |
| Stroke | 10 (8.1) |
| Transient ischaemic attack | 11 (8.9) |
| Diabetes mellitus | 23 (17.7) |
| Kidney disease | 21 (16.9) |
| Liver disease | 10 (8.1) |
| **Type of arrhythmia/ECG abnormality** |  |
| **QTp associated** | **95 (76.6)** |
| TdP, VF, cardiac arrest | 79 (63.7) |
| QTp>500ms without symptoms | 9 (7.3) |
| QTp (≥ 450ms in males or ≥470ms in females) with syncope | 7 (5.7) |
| **Not associated with QTp** | **29 (23.4)** |
| VT/VF | 28 (22.6) |
| Exacerbation of pre-existing VT only | 1 (0.8) |

IQR = interquartile range; QTp = QT interval prolongation; TdP = torsade de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia. \*Self-reported with validation from patient’s hospital notes (where available).**Table 2.** Drugs culpable in proarrhythmia cases, stratified by risk of QT prolongation and/or torsade de pointes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug Name** | **ATC Code** | **Drug Type** | **Number of drug exposures** | **%** |
| **Known risk** |  |  |  |  |
| Amiodarone | C01BD01 | Antiarrhythmic | 40 | 24.2 |
| Sotalol | C07AA07 | Beta-blocking agent / antiarrhythmic | 25 | 15.2 |
| Flecainide | C01BC04 | Antiarrhythmic | 23 | 13.9 |
| Citalopram | N06AB04 | Antidepressant | 7 | 4.2 |
| Erythromycin | J01FA01 | Antibacterial | 5 | 3.0 |
| Clarithromycin | J01FA09 | Antibacterial | 4 | 2.4 |
| Disopyramide | C01BA03 | Antiarrhythmic | 4 | 2.4 |
| Domperidone | A03FA03 | Propulsive | 4 | 2.4 |
| Fluconazole | J02AC01 | Antimycotic | 2 | 1.2 |
| Thioridazine | N05AC02 | Antipsychotic | 2 | 1.2 |
| Ciprofloxacin | J01MA02 | Antibacterial | 1 | 0.6 |
| Haloperidol | N05AD01 | Antipsychotic | 1 | 0.6 |
| Methadone | N07BC02 | Drug used in addictive disorders | 1 | 0.6 |
| Pimozide | N05AG02 | Antipsychotic | 1 | 0.6 |
| **Possible risk** |  |  |  |  |
| Venlafaxine | N06AX16 | Antidepressant | 3 | 1.8 |
| Antihistamine | R06A | Antihistamine | 1 | 0.6 |
| Capecitabine | L01BC06 | Antimetabolite | 1 | 0.6 |
| Clomipramine | N06AA04 | Antidepressant | 1 | 0.6 |
| Olanzepine | N05AH03 | Antipsychotic | 1 | 0.6 |
| Tamoxifen | L02BA01 | Anti-oestrogen | 1 | 0.6 |
| **Conditional risk** |  |  |  |  |
| Furosemide | C03CA01 | Diuretic | 5 | 3.0 |
| Amitriptyline | N06AA09 | Antidepressant | 3 | 1.8 |
| Bendroflumethiazide | C03AA01 | Diuretic | 2 | 1.2 |
| Fluoxetine | N06AB03 | Antidepressant | 2 | 1.2 |
| Amisulpiride | N05AL05 | Antipsychotic | 1 | 0.6 |
| Paroxetine | N06AB05 | Antidepressant | 1 | 0.6 |
| Quinine | P01BC01 | Antimalarial | 1 | 0.6 |
| Trazodone | N06AX05 | Antidepressant | 1 | 0.6 |
| **Drugs to Avoid in cLQTS** |  |  |  |  |
| Trimethoprim | J01EA01 | Antibacterial | 1 | 0.6 |
| **No known risk** |  |  |  |  |
| Digoxin\* | C01AA05 | Cardiac glycoside | 4 | 2.4 |
| Propafenone | C01BC03 | Antiarrhythmic | 3 | 1.8 |
| Cetirizine# | R06AE07 | Antihistamine | 1 | 0.6 |
| Chlorpheniramine | R06AB02 | Antihistamine | 1 | 0.6 |
| Dosulepin | N06AA16 | Antidepressant | 1 | 0.6 |
| Lofexidine† | N07BC04 | Drug used in addictive disorders | 1 | 0.6 |
| Loratadine | R06AX13 | Antihistamine | 1 | 0.6 |
| Procaine | S01HA05 | Local anaesthetic | 1 | 0.6 |
| Theophylline | R03DA04 | Drug for obstructive airways disease | 1 | 0.6 |
| Thiazide | C03 | Diuretic | 1 | 0.6 |
| Timoptol\* | C07AA06 | Beta-blocking agent | 1 | 0.6 |
| Statin | C10A | Lipid modifying agent | 1 | 0.6 |
| Verapamil# | C08DA01 | Calcium-channel blocker | 1 | 0.6 |
| **Unspecified** | - | - | 2 | 1.2 |
| **Total** | **-** | **-** | **165** | **100.0** |

\* Contributed to bradycardia

# Not classified – these drugs have been reviewed by CredibleMeds, however classification could not be performed based on the evidence available and there is no indication the drugs are free of risk of QTp/TdP

† Under active review for possible risk of QTp/TdP

**Table 3.** Drug Combinations Culpable in Cases of Proarrythmia

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug 1** | **Drug 2** | **Drug 3** | **Drug 4** | **Drug 5** | **Number of**  **Patients with combination** | **Potential DDI** | **Number of Drugs** | | | | |
| **Known risk** | **Possible risk** | **Conditional risk** | **P450 inhibitors** | **P450 inducers** |
| Amiodarone | Furosemide |  |  |  | 3 | None | 1 | 0 | 1 | 1 | 0 |
| Citalopram | Flecainide |  |  |  | 2 | QTp | 2 | 0 | 0 | 1 | 0 |
| Amiodarone | Amitriptyline |  |  |  | 1 | QTp | 1 | 0 | 1 | 1 | 0 |
| Amiodarone | Digoxin |  |  |  | 1 | Cardiotoxic | 1 | 0 | 0 | 1 | 0 |
| Amiodarone | Sotalol |  |  |  | 1 | QTp | 2 | 0 | 0 | 1 | 0 |
| Amiodarone | Domperidone |  |  |  | 1 | QTp | 2 | 0 | 0 | 1 | 0 |
| Amiodarone | Flecainide |  |  |  | 1 | QTp | 2 | 0 | 0 | 1 | 0 |
| Amiodarone | Disopyramide |  |  |  | 1 | QTp | 2 | 0 | 0 | 1 | 0 |
| Amiodarone | Statin |  |  |  | 1 | Other | 1 | 0 | 0 | 1 | 0 |
| Amiodarone | Trimethoprim |  |  |  | 1 | QTp | 1 | 0 | 0 | 2 | 0 |
| Amiodarone | Erythromycin |  |  |  | 1 | QTp | 2 | 0 | 0 | 2 | 0 |
| Bendroflumethiazide | Venlafaxine |  |  |  | 1 | None | 0 | 1 | 1 | 0 | 0 |
| Bendroflumethiazide | Cetirizine |  |  |  | 1 | None | 0 | 0 | 1 | 0 | 0 |
| Chlorpheniramine | Olanzepine |  |  |  | 1 | Other | 0 | 1 | 0 | 1 | 0 |
| Ciprofloxacin | Tamoxifen |  |  |  | 1 | None | 1 | 1 | 0 | 1 | 0 |
| Clarithromycin | Fluconazole |  |  |  | 1 | QTp | 2 | 0 | 0 | 2 | 0 |
| Clomipramine | Dosulepin |  |  |  | 1 | QTp | 0 | 1 | 0 | 1 | 0 |
| Digoxin | Timoptol |  |  |  | 1 | Cardiotoxic | 0 | 0 | 0 | 0 | 0 |
| Disopyramide | Flecainide |  |  |  | 1 | QTp | 2 | 0 | 0 | 0 | 0 |
| Flecainide | Furosemide |  |  |  | 1 | None | 1 | 0 | 1 | 0 | 0 |
| Paroxetine | Thiazide |  |  |  | 1 | Conditional | 0 | 0 | 1 | 1 | 1 |
| Sotalol | Fluoxetine |  |  |  | 1 | QTp | 1 | 0 | 1 | 1 | 0 |
| Methadone | Venlafaxine |  |  |  | 1 | QTp | 1 | 1 | 0 | 1 | 0 |
| Thioridazine | Fluoxetine |  |  |  | 1 | QTp | 1 | 0 | 1 | 0 | 0 |
| Amiodarone | Domperidone | Fluconazole |  |  | 1 | QTp | 3 | 0 | 0 | 2 | 0 |
| Amiodarone | Furosemide | Digoxin |  |  | 1 | Cardiotoxic | 1 | 0 | 1 | 1 | 0 |
| Amiodarone | Clarithromycin | Antihistamine | Digoxin |  | 1 | QTp | 2 | 1 | 0 | 2 | 0 |
| Haloperidol | Clarithromycin | Citalopram | Amitriptyline |  | 1 | QTp | 3 | 0 | 1 | 3 | 0 |
| Citalopram | Domperidone | Amitriptyline | Procaine | Quinine | 1 | QTp | 2 | 0 | 2 | 1 | 0 |

DDI = drug-drug interaction; QTp = QTc interval prolongation

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