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The role of QT-prolonging medications in a forensic autopsy study from Western Denmark

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ABSTRACT

Medication-induced prolongation of the QT-interval (miQTP) can lead to cardiac arrhythmia. Our aim was to investigate the prevalence of forensic autopsy cases where fatal cardiac arrhythmia related to treatment with QT-prolonging medications (QT-PMs) could be suspected. We performed a cross-sectional study of 741 forensic autopsies undertaken at our institution in non-drug addicts aged 15 years or above from 2017 to 2019. We defined a high risk of miQTP by one detected QT-PM in a concentration above therapeutic level, or two or more detected QT-PMs in post mortem blood. We reviewed the autopsy reports from cases with a high miQTP-risk to identify cases with no other apparent cause of death. We discarded suicides and cases with lethal levels of QT-PMs. We identified 167 cases (22.5%) with high risk of miQTP, and discarded 36 suicides (4.9%) and 7 (0.9%) with lethal levels of QT-PMs. Apart from a high risk of miQTP, no other apparent explanation of the cause of death was present in seven (0.9%). In 18 cases (2.4%) with high miQTP-risk, the cause of death was primarily attributed to cardiac changes other than acute cardiovascular events. In conclusion, 22.5% had a high risk of miQTP, and fatal cardiac arrhythmia related to treatment with QT-PMs could be suspected in 0.9%. However, a genetic pro-arrhythmic background could not be excluded in our study. Furthermore, it is possible that QT-PMs could have played a role in some of the 2.4% of cases where the cause of death was mainly attributed to cardiac changes and the risk of miQTP was high.

1. Introduction

Medication-induced prolongation of the QT-interval on the electrocardiogram (ECG) is an important safety issue for several medications [1]. The clinical significance of a prolonged QT-interval lies in its potential to convert heart rhythm into the polymorphic ventricular tachycardia, torsades de pointes (TDP) [2,3]. Most medications capable of inducing prolonged QT-interval (QT-PMs) lengthen the QT-interval by blocking the rapid delayed rectifier-potassium channels, which are responsible for repolarization of cardiac muscles, or by altering protein channels [3–5]. TDP associated with prolonged QT-interval may be asymptomatic or elicit symptoms including palpitations, dizziness, seizures, or syncope [2,3]. It often resolves spontaneously, but may degenerate into life-threatening ventricular fibrillation and cause sudden death [2,6].

Case-control studies have shown an association between use of QT-PMs and increased mortality [6,7], and although the risk of medication-induced arrhythmias is low in the general population, it increases when multiple QT-PMs are used simultaneously [8,9]. Furthermore, the risk of sudden death may be significantly higher in certain subgroups such as patients with schizophrenia, elderly, patients with asthma, and hospitalized patients with cardiac disease [10]. There is no classification code for death due cardiac arrhythmia related to medication-induced QT-prolongation (miQTP) [11], and the frequency of such deaths is difficult to establish, because peri-mortal recordings of cardiac heart rhythm in persons dying unexpectedly are very rarely available. Furthermore, sudden death due to cardiac arrhythmia may occur in absence of QT-PMs due cardiac disease including inherited disease as congenital long QT-syndrome, which makes it difficult to interpret the isolated role of QT-prolonging medications in forensic casework. On the other

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hand, QT-PMs significantly increase the risk of cardiac arrhythmia in persons with congenital long QT-syndrome [11,12].

We often detect QT-PMs in toxicological analyses of post mortem blood in forensic autopsies, and our hypothesis was that cardiac arrhythmia caused by miQTP might cause death in a number of cases. Especially among those where a QT-PM is found in a concentration above therapeutic levels, or where two or more QT-PMs are found, because treatment with a high dose or more than one QT-PM implies a higher risk for miQTP [11]. Our aim was to elucidate the prevalence of cases in which we found a high risk of miQTP, and no other explanation for the cause of death among adults who were not drug addicts. This could give an impression about how often cardiac arrhythmia occurs related to medical treatment with QT-PMs. We find this knowledge important due to the high level of concern and many precautions associated with clinical use of QT-PMs.

2. Methods

2.1. Design and study population

We used the STROBE-checklist [13] for preparation of the manuscript. The study was a cross-sectional study of all forensic autopsy cases performed in 2017–2019 at our institution. Drug addicts and cases with age < 15 years were excluded. We used the same definition of a drug addict as in previous studies [14]. Briefly, a person with current or past abuse of narcotic drugs such as e.g. heroin, methadone, cocaine, and amphetamine was considered a drug addict. Persons who only abused cannabis were not defined as drug addicts in our study. Drug addicts make up a significant part of Danish forensic autopsy cases, and often die from accidental overdose of methadone, which is a QT-PM [14]. Fatal poisonings in drug addicts in Denmark are well described [14], and we chose not to include them.

2.2. Definition of miQTP-risk

We defined high risk of miQTP by the detection of one QT-PM in a concentration above therapeutic level, or by the detection of two or more QT-PMs in postmortem peripheral blood. Low risk of miQTP was defined by detection of one QT-PM in a concentration at or below therapeutic levels. If one QT-PM was detected but not quantified due to e.g. lack of suitable material, we also designated the case as having low risk for miQTP. Cases in which a full toxicological analysis was performed and no QT-PMs were detected were defined as having no risk of miQTP. Cases with no full toxicological analysis were defined as having unknown risk of miQTP.

2.3. Definition of QT-PMs

QT-PMs were defined in accordance with the list from CredibleMeds® [1]. Amiodarone was not counted if only used for resuscitation. We entered nortriptyline and paliperidone if amitriptyline and risperidone, respectively, were absent, or if medical use of both the parent medication and the metabolite was evident. We also noted if use of any QT-PMs not included in our screening method was stated in the preliminary autopsy report.

2.4. Categorization of the main cause of death

We classified all cases into categories based on the main cause of death according to the primary SNOMED term in the autopsy report as shown in Table 1. Cases with significant atherosclerosis found on autopsy also followed this rule.

2.5. Algorithm for identification of cases with high risk of miQTP and no other apparent cause of death

We reviewed the descriptive conclusion and the SNOMED classification of the cause of death in all cases, and discarded cases in which the manner of death was suicide to focus on unintentional cases related to treatment. Furthermore, we discarded cases, in which we found lethal concentrations of QT-PMs, because other mechanisms than cardiac arrhythmia such as sedation, respiratory depression, and hypotension may result in death in these cases. Finally, we excluded cases with unknown cause of death, which were unassessable because another indeterminable cause was suspected, or the condition of the body did not allow to draw conclusions.

We strongly suspected QT-PMs to contribute to death in cases with no other apparent cause of death. Furthermore, as cardiac disease is a known risk factor for miQTP [15] we speculated that QT-PMs could contribute in cases where death was attributed to cardiac abnormalities other than acute cardiovascular events.

As a control measure, we also reviewed cases with low risk of miQTP using the same algorithm.

2.6. Data and forensic autopsies

All data used for comparisons of groups were extracted from the autopsy reports, and included detected QT-PMs, sex, height, body weight, heart weight, presence of significant or mild to moderate coronary atherosclerosis as noted by the forensic pathologist, manner of death, cause of death, and psychiatric disease.

In Denmark, cases of unexpected deaths, persons found dead, and deaths suspected to be related to accidents or crimes are reported to the police who decides if a forensic autopsy should be performed in accordance with the Danish Act of Health [16]. Ministry of Justice has decided that an autopsy is mandatory when death is related to drug abuse. Autopsies are performed according to the ISO 17020 accredited procedure of the department. In cases of suspected sudden cardiac death, current guidelines are followed [17]. The presence of significant coronary atherosclerosis is defined by luminal stenosis above 75% [17,18]. For assessment of abnormal cardiac weight we use reference values from the study by Kitzman et al. [19].

The toxicological analysis is performed by screening for toxic compounds, illegal and legal medications and some of their metabolites using protein precipitation followed by ultra-performance liquid chromatography with high-resolution time-of-flight mass spectrometry (UPLC-HRTOF-MS). The method detects approximately 700 substances. Detected medications are quantified by ultra-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS). The analyses are performed according to the international standard ISO 17025. The output for use in casework is a report of the detected medications, their concentrations, and an interpretation of the concentration level (below, at, or above normal treatment levels, toxic or lethal) of each medication based on a synthesis of original articles with concentration levels for each individual medication and literature with compilations of data [20–23]. We also state in the report if any medication known to be used by the concerned individual is not included in the initial screening.

2.7. Ethical considerations

The study was registered at the University, and data were handled in accordance with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act. According to the Consolidation Act on Research Ethics Review of Health Research Projects, Consolidation Act number 1083 of September 15th 2017,

Table 1
Classification of the main cause of death.

Category	SNOMED term for main cause of death
Disease	Any term describing a manifestation of an acute or chronic disease
Acute cardiovascular event	Myocardial rupture, myocardial infarction, coronary thrombosis, coronary artery bleeding, aortic rupture, hemopericardium, hemothorax, myocarditis, pulmonary embolism
Other cardiovascular disease	Coronary atherosclerosis, cardiac enlargement, heart failure, cardiac arrhythmia obs. pro, cardiac fibrosis, unspecified cardiovascular disease.
Other disease	Terms describing any manifestation of acute or chronic disease other than those mentioned in the category of acute cardiovascular event and other cardiovascular disease
Poisoning	Term describing poisoning with medication, carbon monoxide, or alcohol. A few cases of adverse effect to a medication such as anaphylactic reactions were included in this category.
Trauma	Terms describing consequences of any extrinsic effect on the body such as sharp or blunt force, thermal injury, drowning, obstruction or compression of airways
Unknown	Unknown

Classification of the main cause of death according to the SNOMED term of the main cause of death.

section 14 (2) the project did not need approval from the Committees on Health Research Ethics. The Central Denmark Region Ethics Committee confirmed this.

2.8. Statistics

We entered data in REDCap electronic data capture tool [24]. Continuous variables with normal distribution (tested with shapiro-wilks test) were expressed as mean ± standard deviation, non-normally distributed were expressed as median [25th-75th percentile], and categorical variables were expressed in percentages. Differences in characteristics between two groups were calculated using Student´s *t*-test, Wilcoxon's rank sum test, or $\chi 2$ test, where appropriate. A p-value <0.05 was considered statistically significant. Missing data were not imputed. We used STATA 16, Stata Corp, Texas, for statistical analysis.

3. Results

In 2017–2019, 1028 autopsies were performed. We excluded 254 drug addicts and 33 cases with age below 15 years, and included 741 cases (Fig. 1). A total of 167 cases (22.5%) had a high risk of miQTP. Fig. 2 shows the flow of cases fulfilling the criteria for a high risk of miQTP, and the category of the main cause of death in the different miQTP-risk groups. The prevalence of women, psychiatric disease and suicides, as well as BMI was higher in cases with high miQTP risk compared to those with no or low risk (Table 2). Furthermore, high risk of miQTP was associated with a higher prevalence of death due to poisoning, and a lower prevalence of death caused by trauma and unknown causes (Fig. 2). The process of sorting cases with high miQTP risk is shown in Fig. 1. In seven cases (0.9%), no other apparent cause of death was found. Their median age was 41 [37–55] years. Five (71.4%) of the seven cases were female, and the median number of detected QT-PMs were 3 [2,3]. Five (71.4%) had been seen

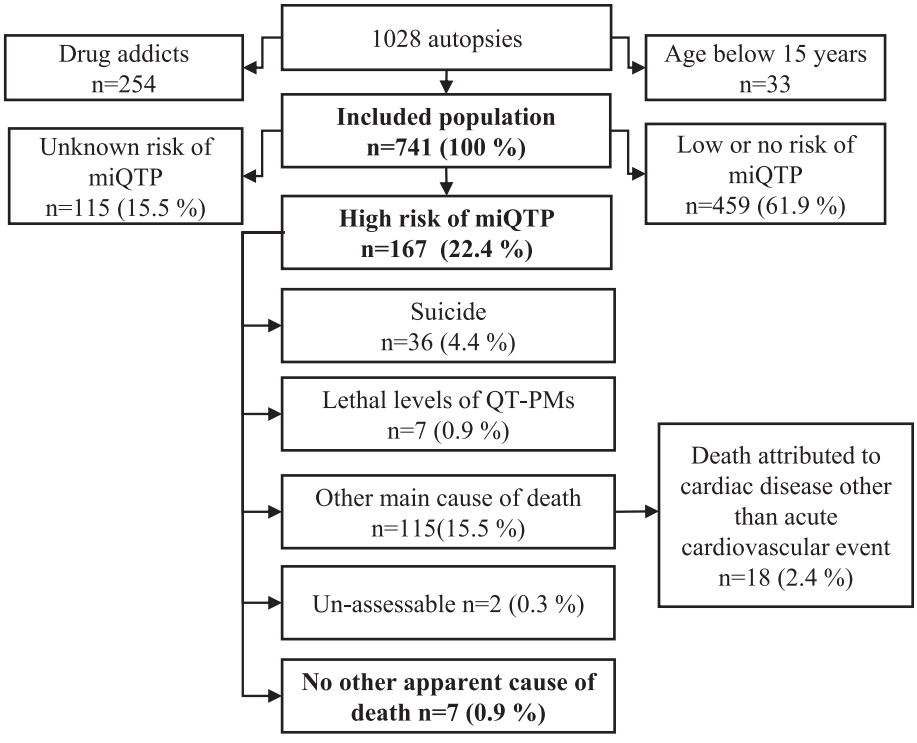

Fig. 1. Overview of case-selection in the study. Flow chart of excluded cases, cases with high risk of miQTP, and the process of sorting them according to the manner and main cause of death. Abbreviations: miQTP: medication-induced QT-prolongation, n = number.

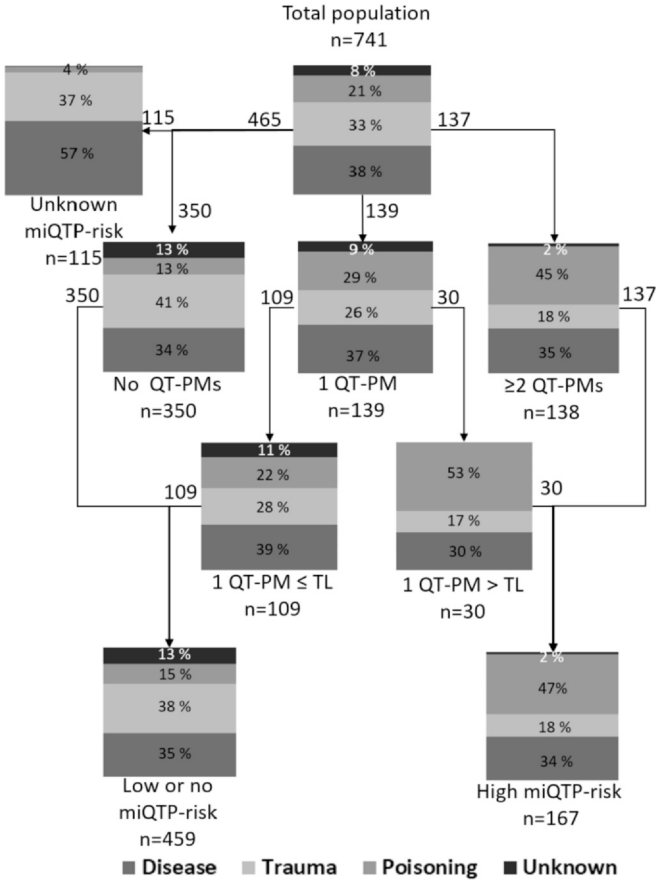

Fig. 2. Flowchart and causes of death according detection of QT-PMs and risk of miQTP. Flowchart showing the number of cases in the different miQTP-risk groups including the number of cases fulfilling the criteria for high risk based on either one detected QT-PM in concentrations above therapeutic level, or two or more QT-PMs, respectively. Bars show the percentage of cases in each group in whom the cause of death was categorized as disease, trauma, poisoning, or unknown, respectively. Abbreviations: miQTP: medication-induced QT-prolongation, QT-PMs: QT-prolonging medications, TL: therapeutic levels, n = number.

alive the day before found dead or their death was witnessed. Two cases were referred for examination of suspected inherited cardiac disease. Information about initiation of treatment with the detected QT-PMs was unavailable in most cases.

Table 3 details the cause of death in the 115 cases with other main causes. In 18 cases (2.4%), the cause of death was primarily attributed to cardiac changes other than acute cardiovascular events. In some of these cases, other contributing diseases or circumstances including QT-PMs were mentioned in the descriptive conclusion about the cause of death. The median age of these 18 cases was 63 [54–72] years, 8 (44%) were female. Four (22.2%) and 11 (61%) had significant and mild-to moderate coronary atherosclerosis, respectively, and 12 (66%) had heart-to-body weight ratio larger than the upper 95th limit of normal. [19] In five cases (27.7%), it was stated that a QT-PM had been initiated recently or a few days to weeks before death.

3.1. Review of cases with low risk of miQTP

Suicide was the manner of death in 13 (11.9%) of the 109 cases. An acute cardiovascular event, other disease, accidental trauma or poisoning was the main cause of death in 13 (11.9%), 19 (17.3%), 20 (18.3%), and 22 (20.1%), respectively. Thus, in 22 (20.1%), the cause of death was attributed to other cardiac disease (n = 10 (9.2%)) or was unknown (n = 12 (11.0%)). In 16 of these (17.1%), the QT-PM was a diuretic used to treat hypertension or chronic heart failure, the QT-PM was detected in subtherapeutic concentration, other causes of death could not be excluded due to the condition of the body, or other causes were considered as likely as cardiac arrhythmia related to miQTP. Thus, a non-diuretic QT-PM was detected in three cases where no other apparent cause of death was present, and in three cases, where death was mainly attributed to other cardiac disease than an acute cardiovascular event.

3.2. The detected QT-PMs

Antidepressants followed by antipsychotics and opioids were the most frequently detected groups of QT-PMs in both cases with low and high risk of miQTP (Fig. 3a+b). However, diuretics were relatively more prevalent in the low-risk group. Furosemide and quetiapine were the most frequently detected individual QT-PMs in the low and high-risk group, respectively.

In the seven cases with high miQTP-risk and no other apparent cause of death, 14 different QT-PMs were detected 18 times. Antipsychotics and antidepressants were most frequently detected (eight and six times, respectively). Antibiotics or antiemetics were detected in three.

In 18 cases (2.4%), the preliminary autopsy report mentioned a total of 23 QT-PMs not included in our screening. Ten of the cases were already included in the group with high risk of miQTP, and the cause of death was most likely unrelated to QT-PMs in the majority of the remaining eight cases. The concerned QT-PMs were predominantly antibiotics, proton-pump inhibitors, and diuretics.

Table 2
Characteristics of cases with high and low risk of miQTP.

		Total study group	No or low risk of miQTP	High risk of miQTP	P-value (high vs. no or low risk)
Number of cases	n	741	459	167	
Age	Years	55 [43–68]	54 [45–66]	54 [45–68]	0.2
Female sex	n (%)	269 (36.3)	132 (28.7)	99 (59.3)	< 0.001
BMI	Kg/m^2	25.9 [22.2–30.0]	25.3 [21.5–28.6]	27.9 [23.8–33.4]	< 0.001
Psychiatric disease	n (%)	173 (23.3)	71 (15.5)	91 (54.5)	< 0.001
Suicide	n (%)	85 (11.5)	44 (9.6)	36 (21.6)	< 0.001
Coronary atherosclerosis	n (%)	403 (54.4)	241 (52.5)	88 (52.8)	1.0
Significant coronary atherosclerosis	n (%)	112 (15.1)	63 (13.7)	21 (12.6)	0.7
Heart weight / bodyweight	%	0.52 [0.45–0.62]	0.53 [0.45–0.62]	0.50 [0.42–0.61]	0.1
Death caused by acute cardio-vascular event	n (%)	72 (9.7)	31 (6.7)	10 (6.0)	0.7
Death caused by other cardiac disease	n (%)	75 (10.2)	47 (10.2)	21 (12.6)	0.4
n of QT-PMs		0[0,1]	0 [0]	2 [2,3]	–

Characteristics of cases according risk of miQTP. The total study group includes 115 cases with unknown risk of miQTP in addition to cases with no, low, or high risk of miQTP. Numerical data are expressed as medians with interquartile range [Q1-Q3]. [a]: Data for BMI was available in n = 431 in the Low risk group, and n = 166 in the High risk group. [b]: Data for heart weight/bodyweight was available in n = 426 in the no or low risk group, and n = 165 in the high risk group. Abbreviations: miQTP: medication-induced QT-prolongation, QT-PMs: QT-prolonging medications, n = number.

Table 3
Specification of the cause of death in the 115 cases with high risk of miQTP and other main cause of death.

Category	n (%)	Main cause of death	n (%)
Disease			
Acute cardiovascular event	10 (8.7)	Acute myocardial infarction	3 (2.6)
		Pulmonary embolism	3 (2.6)
		Hemopericardium or infection	4 (3.5)
Other cardiac disease	18 (15.6)	Hypertrophy, coronary atherosclerosis and/or valvular pathology	18 (15.6)
Other disease	25 (21.7)	Gastro-intestinal disease	9 (7.8)
		Pulmonary disease	6 (5.2)
		Cerebral disease	4 (3.5)
		Sepsis	3 (2.6)
		Other	3 (2.6)
Trauma	24 (20.9)	Drowning	5 (4.3)
		Cranial injury	7 (6.1)
		Other injury	12 (10.4)
Poisoning	38 (33.0)	Opioids (including tramadol*), sedatives and/or alcohol	18 (15.7)
		Other non-QT-PMs with significant contribution	14 (12.2)
		Carbon monoxide poisoning	4 (3.5)
		≥2 QT-PMs in non-lethal concentrations plus other contributing disease	2 (1.7)

Outline of the different main causes of death after exclusion of suicides, cases with lethal levels of QT-PMs, and unassessable cases, in the group of cases with high miQTP-risk. *Tramadol poisoning occurred in three cases. Abbreviations: miQTP: medication-induced QT-prolongation, QT-PMs: QT-prolonging medications, n = number.

4. Discussion

The main finding of our study was that 22.5% of non-drug addict autopsy cases had a high risk of miQTP according to our definition. However, no alternative cause was apparent in only 0.9%, and a fatal cardiac arrhythmia caused by treatment with QT-PMs could be strongly suspected in these. In the majority of these seven cases, age was between 20 and 55 years. Our institution covers an area where approximately 3600 deaths occurred in people aged between 20 and 55 years in 2017–2019 [25]. Assuming that all cases of possible fatal cardiac arrhythmia had an autopsy performed in this period, the seven cases would account for approximately 0.2% of deaths in this age group. However, a recent study has indicated that forensic autopsy may be omitted even in young subjects possibly dying from cardiac disease [17]. Thus, the proportion of relevant cases represented in our study group is unknown. Also, whether the cause of death was actually cardiac arrhythmia cannot be confirmed. Five of the cases were observed alive shortly before or during death, which is in accordance with the usual definition of sudden cardiac death [18]. In the remaining cases, the time since last observed alive was not specified. Such cases would normally not be included in studies of sudden cardiac death, but we find them relevant to mention due to the absence of another likely explanation for the cause of death. However, even if we were able to confirm cardiac arrhythmia as the cause of death in our seven cases, a recent study showed that one third of a study population with acquired long QT-syndrome carried

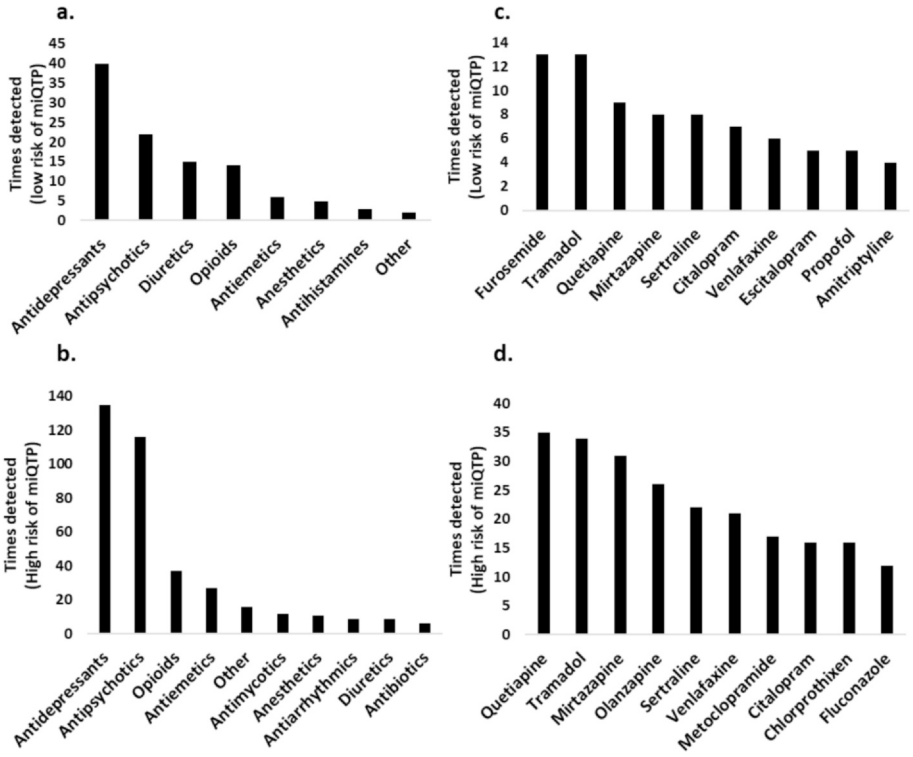

Fig. 3. Detected QT-PM classes and individual QT-PMs according to risk of miQTP. Most frequently detected QT-PM classes (a.) and individual QT-PMs (b.) in cases with low risk of miQTP, and high risk of miQTP (c. and d.), respectively. Bars indicate the total number of times a medication class or medication, respectively, was detected in the postmortem blood of cases in each group. Abbreviations: miQTP: medication-induced QT-prolongation, QT-PMs: QT-prolonging medications.

genetic mutations known to prolong the QT-interval [26,27]. Therefore, examination for inherited cardiac diseases including long QT-syndrome should be done to clarify if an underlying pro-arrhythmic condition contributed. Unfortunately, results of such genetic examinations were unavailable in most of our cases.

Cardiac changes other than acute cardiovascular events according to our definition most likely explained the cause of death in 18 of the cases with high risk of miQTP. In a guideline for evaluation of sudden cardiac death, the most common substrates of sudden cardiac death is divided into certain, highly probable, or uncertain [18]. We were not able to classify the cardiac findings of the 18 cases into these categories based on the available data in the autopsy reports, but we assume that they would fall into the category of highly probable or uncertain. According to the guideline, consideration of other contributing factors including QT-PMs are important in such cases [18], and thus, we can only speculate towards that QT-PMs could have contributed to death in some of these 18 cases. Of notice, the prevalence of cases in which the cause of death was categorized as other cardiac disease than acute cardiovascular events was not higher in cases with high risk of miQTP compared to those with no or low risk. This was unexpected, because cardiac disease is known to increase the risk for miQTP [15], and a case-control study restricted to persons with coronary artery disease has shown that cases experiencing sudden cardiac death were more likely to use QT-PMs. However, the size and the heterogeneity of our study population may explain why we could not confirm this association.

Other diseases such as pneumonia or cancer are also risk factors for miQTP [28–32]. Furthermore, associations between miQTP and an increased risk of drowning has been suggested [33]. Thus, QT-PMs could have contributed to death in some of our cases with high risk of miQTP where a manifestation of disease or drowning was apparently the main cause of death. However, we considered the basis for a contributing role of QT-PMs in these cases too uncertain. Furthermore, we identified a few cases in our group with low risk of miQTP, in which we detected a relevant QT-PM in therapeutic levels and no other apparent cause of death was found. We cannot exclude that the QT-PM may have been the determining factor in these cases. However, miQTP is considered less likely to occur with standard treatment doses of QT-PMs [11], and therefore, we also consider the role of the detected QT-PM uncertain in these cases. On the other hand, it has been shown that some QT-PMs are up-concentrated in cardiac tissue [34], meaning that a low or therapeutic concentration in blood cannot exclude a relevant exposure of the heart.

Death related to QT-PMs may occur shortly after initiation of treatment [35]. In our study, a QT-prolonging antibiotic or antiemetic was present in three of the seven cases with high risk of miQTP and no other apparent cause of death. These medications are for short-term use, and thus, we can assume initiation shortly before death. Furthermore, information about recent initiation of a QT-PM was mentioned in five of the 18 cases with high risk of miQTP and “other cardiac disease” as the most likely cause of death. This temporal relationship strengthen the suspicion of a causal relationship. However, although our available information on this aspect was scarce, our data may suggest that sudden death related to miQTP can occur unrelated to initiation or dose-escalation of a QT-PM. This might be due to e.g. intercurrent electrolyte disturbances, fluctuations in sex hormones [36], bradycardia, or poor compliance. Thus, the response to QT-PMs is patient specific and may vary over time.

Several medications are defined as QT-PMs without further subdivision in our study. The list that we used divides medications into drugs with conditional, possible, and known risk of TDP, respectively [1]. Furosemide, which dominated in our group with low risk of miQTP is classified as a medication with conditional risk, and when we detect a diuretic as the only QT-PM in a case, we do not usually suspect miQTP. In contrast, the significance of the groups that dominated in our high risk group such as antidepressants and antipsychotics is well-documented [37–40]. Based on the detected groups of QT-PMs in the low- and high miQTP-risk groups, and our review of cases in the low-risk group, we think that our criteria defining a high risk of miQTP may be useful in future studies of the role of QT-PMs in forensic autopsies. However, it may be relevant to include cases with one detected non-diuretic QT-PM in therapeutic concentration.

Our finding that 22.5% of these non-drug addict cases fulfilled our criteria for high risk of miQTP, and that at least one QT-PM was present in 37% underlines that forensic post-mortem toxicological investigations should not be limited to drugs of abuse but should also include QT-PMs. Due to the concerns about sudden cardiac death in patients treated with QT-PMs, we think more research in autopsy cases is relevant to improve knowledge about the prevalence and characteristics of this phenomenon. However, discussion about when to suspect contribution from QT-PMs to the cause of death, and how to code it on the death certificate could be valuable for the conduction of future studies.

4.1. Study limitations

The inability to assess electrolyte disturbances and cardiac rhythm before death as well as limitations to the interpretation of postmortem medication concentrations, due to e.g. postmortem redistribution [41] are immanent limitations of our study. Furthermore, we did not reevaluate microscopic organ specimens for the purpose of the study.

Our screening did not cover all QT-PMs mentioned in the preliminary autopsy reports. However, we reviewed all cases with mentioned medications that were screened for and found it unlikely that we missed any relevant cases due to this circumstance. Furthermore, a full toxicological analysis was not done in all cases. However, a toxicological analysis is most often omitted in cases where autopsy findings determine the cause of death, and therefore we consider the risk of missing relevant cases in this group to be low.

5. Conclusions

Although 22.5% of non-drug addict forensic autopsy cases had high risk of miQTP according to our definition, no apparent explanation other than high risk of miQTP was found in only 0.9% of cases. A fatal cardiac arrhythmia related to treatment with QT-PMs could be suspected in these. Furthermore, death primarily attributed to cardiac findings other than an acute cardiovascular event in cases with high risk of miQTP occurred in 2.4%. QT-PMs could possibly have contributed to death in some of these.

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CRediT authorship contribution statement

H. Ahmed: Data curation, Conceptualization, Writing - original draft. **M.K. Larsen:** Data curation, Conceptualization, Writing - review & editing. **M.R. Hansen:** Data curation, Conceptualization, Writing - review & editing. **C.U. Andersen:** Data curation, Conceptualization, Data-analysis, Writing - original draft, Writing - review & editing.

Declarations of interest

The authors have no conflicts of interest to declare.

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