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QTc prolongation and prognosis in patients with suspected poisoning in the emergency department – a transnational propensity score matched cohort

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ABSTRACT

OBJECTIVES: Poisoning is a frequent cause of admission to the emergency department (ED), and may involve drugs known to prolong the QT interval. The aims of this study were to describe the prevalence of QTc prolongation among ED patients with suspected poisoning and to calculate the absolute and relative risk of mortality or cardiac arrest associated with a prolonged QTc interval.

METHODS: We performed a register-based cohort study, including all adult first time contacts with suspected poisoning to the ED of two Swedish hospitals (January 2010 to December 2014) and two Danish hospitals (March 2013 to April 2014). We used propensity score matching to calculate hazard ratios (HR) for all-cause mortality or cardiac arrest (combined endpoint) within 30 days after contact comparing patients with a prolonged QTc interval (≥450 ms men, ≥460 ms women) with patients with a QTc interval of <440 ms.

RESULTS: Among all first-time contacts with suspected poisoning that had an ECG recorded within four hours after arrival (n = 3869), QTc prolongation occurred in 6.5%. The overall mortality after a 30-day follow-up period was 0.8% (95% CI, 0.6-1.2), with an absolute risk of mortality or cardiac arrest in patients with QTc prolongation of 3.2% (95% CI, 1.4-6.1). A prolonged QTc interval on arrival was associated with a HR of 3.6 (95% CI, 1.0-12.2).

CONCLUSION: In the ED, a prolonged QTc interval in patients arriving with suspected poisoning seems to be associated with a three-fold increased risk of 30-day all-cause mortality or cardiac arrest.

Strengths and limitations of the study

Patients were included from four different hospitals – two Swedish and two Danish.

Propensity score matching was used to adjust for several confounders.

Subgroups analysis was not possible due to a small number of events.

The included ECGs were all automatic readouts and the length of the QT interval was not confirmed manually.

INTRODUCTION

Poisoning is a frequent cause of admission to the emergency department (ED),[1,2] and involves a variety of different drugs and substances. A wide range of drugs have been linked to QTc prolongation,[3] which has been associated with all-cause-mortality, cardiovascular death, and sudden cardiac death.[4-9] As an increased risk of mortality has been documented in patients treated with potential QTc prolonging drugs,[10-13] one may hypothesize that the risk is even higher among poisoned patients. Therefore, cardiac monitoring is recommended in patients poisoned by potentially proarrhythmic agents and drugs that can lead to torsades de pointes.[14]

Only few studies have investigated the relationship between QTc prolongation and adverse outcomes in a population of undifferentiated poisoned patients.[15,16] The absolute and relative risk of mortality and cardiac arrest associated to QTc prolongation in poisoned patients remains unknown. Therefore, we aimed to: (1) describe the prevalence of QTc prolongation found among patients with suspected poisoning in the emergency department; (2) to investigate if QTc prolongation is associated with an increased risk of mortality or cardiac arrest within 30 days after arrival to the emergency department.

MATERIALS AND METHODS

Study design and setting

This is a register-based cohort study. The study is based on ED data from January 1 2010 to December 31 2014 from two Swedish hospitals (Skåne University Hospital, Lund and Helsingborg Hospital) and from two Danish hospitals (Odense University Hospital and the Hospital of South West Jutland, Esbjerg) from March 1 2013 to April 30 2014. In both Denmark and Sweden, the healthcare systems are tax-funded and all residents have free access to healthcare. The University

Hospital Skåne has a contingency population of approximately 310,000, whereas Odense University Hospital covers a population of 290,000 people. The two regional hospitals have a contingency population of 250,000 people (Helsingborg), and 220,000 people (Esbjerg).

Selection of participants

We identified all adults (≥18 years), who arrived to the EDs with suspected poisoning. The contacts were eligible for the main analysis if they had a 12-lead ECG recorded within 4 hours after arrival. A missing QTc interval on the recorded ECG, or a QRS duration of ≥120 ms were both reasons for exclusion. Patients with multiple contacts were included only at their first contact with suspected poisoning within the study period. Information regarding identification of patients with suspected poisoning is outlined in Appendix A.

Data sources

In both Denmark and Sweden, all residents have a unique personal civil registration number, which allows cross-linkage at personal level between databases. We extracted data from several registries: The logistic systems in the ED at the Region of Southern Denmark[17] and Region of Skåne, the electronic central ECG databases at Region of Southern Denmark and Region of Skåne, the Danish National Patient Registry[18] and Region of Skåne Health care databases, the Danish National Prescription Registry,[19] the Swedish Pharmacy Registry,[20] and finally The Danish Civil Registration System[21] and the Swedish Population Register.[22] Further information regarding the data sources is provided in Appendix A.

ECG measurements and definitions

The QT interval was measured at the first ECG recorded after contact to the ED. All the QT intervals were calculated automatically as a median value and stored in either MUSE Cardiology Information System (GE Healthcare) or Philips Diagnostic ECG. The GE Marquette 12SL ECG Analysis Program provided QTc intervals for ECGs recoded in MUSE.[23] ECGs recorded by Phillips were analyzed by the DXL-algorithm.[24] Only QT intervals corrected for heart rate (QTc) was used in our analysis. For correction, we chose the Framingham Formula ($QTc_{Framingham}$ =QT + 0.154 (1-RR)).[25] Additional details about ECG measurements are outlined in Appendix B.

Exposure and outcome

Our primary outcome was a combined endpoint of all-cause mortality or cardiac arrest (defined in Appendix C.1) within 30 days from the day of arrival to the ED. Patients who died in relation to cardiac arrest were classified as dead rather than cardiac arrests. The primary exposure was QTc prolongation, defined as a QTc of ≥450 ms for men and ≥460 ms for women.[26] Patients with a normal QTc length were defined as having a QTc interval of <450 ms (men) or <460 ms (women).

Analysis

The prevalence of QTc prolongation overall, and in relation to specific groups of poisoning was described in a cross-sectional description. In this description, we identified all patients with a discharge diagnosis of poisoning (International Classification of Diseases (ICD-10) codes T36*-T65*, F100*, F110*, F120*, F130*, F140*, F150*, F160*, F170*, F180* or F190* as a primary or secondary diagnosis). All patients, who had a discharge diagnosis of poisoning, were subdivided into five poisoning groups: 1. Analgesics and drugs of abuse, 2. Psychotropic drugs including drugs affecting the central nervous system, 3. Organic and chemical substances, non-medical, 4. Others, and 5. Multidrug (see Appendix C.2).

The association between QTc prolongation and all-cause mortality and cardiac arrest was evaluated using propensity score matching.[27,28] We calculated a propensity score for all included patients by use of logistic regression with QTc ≥450 ms (men) or ≥460 ms (women) as the outcome (binary outcome). Patients with a QTc interval between 440-449 ms (men) and 440-459 ms (women) were excluded in the model to avoid near-overlapping ranges. The following possible confounders were included in the propensity score model: sex, age, comorbidity (measured as Charlson Comorbidity Index[29,30]), history of myocardial infarction or congestive heart failure (Appendix C3. and C.4), prescription of QT prolonging drugs within 90 days (defined in Appendix C.5), heart rate, and study center. We performed a 1:2 parallel balanced nearest neighbor matching without replacement and with a caliper of 0.05.[31] In the matched cohorts, 30-day mortality was modelled using Cox regression.

Statistics

The absolute risk of event in patients with suspected poisoning was calculated overall, for those with QTc prolongation and for those without QTc prolongation. In the propensity score matched cohort, the risk associated with QTc prolongation was estimated as hazard ratios (HR). We estimated 95% confidence intervals based on a binominal distribution. To illustrate the impact of QTc prolongation on 30-days all-cause mortality or cardiac arrest we generated a Kaplan Meier failure curve.

In a sensitivity analysis, we restricted the material to individuals who were both suspected of being poisoned on arrival and received a discharge diagnose of poisoning. The prevalence of QTc prolongation and the propensity score analyses were repeated using the Bazett formula for QT correction.[32]

Statistical analyses were performed using STATA version 14 (StataCorp LP, College Station, Texas). The study was approved by the Danish Data Protection Agency (No. 2008-58-0035, Journal nr. 15/21632) and The Danish Health Authority (No. 3-3013-1031). In consistency with Swedish law the study was approved by the Regional Ethics Committee in Lund and by Region Skåne.

RESULTS

Characteristics of the study cohort

At the four hospitals, we identified a total of 6838 ED contacts with suspected poisoning. After exclusion of those aged <18 years (n=22), an ECG not recorded in an acceptable time-interval (n=1411), multiple contacts within the study period (n=1412), a missing QT interval (n=1), or QRS duration ≥120 ms (n=123) the final cohort comprised 3869 patients with suspected poisoning (48.0% men, median age 38) (Figure 1). Of these, 69.2% (n=2676) had a discharge diagnose of poisoning.

Patients with a prolonged QTc interval were older, had more comorbidity, and more commonly had a history of heart disease than those without QTc prolongation (Table 1).

Table 1: Baseline characteristics of the study population

	All*	Before propensity score matching		After propensity score matching	
		QTc <440 ms (men and women)	Prolonged QTc ≥450 ms (men) ≥460 ms (women)	QTc <440 ms (men and women)	Prolonged QTc ≥450 ms (men) ≥460 ms (women)

N	3869	3296	253	496	248
Sex Male (%)	1859 (48.0)	1634 (49.6)	121 (47.8)	229 (46.2)	119 (48.0)
Age (median, IQR)	38 (25-53)	36 (24-51)	52 (36-68)	53 (37-69)	51 (35-66)
18-50 – n (%)	2747 (71.0)	2444 (74.2)	119 (47.0)	236 (48.0)	119 (48.0)
51-69 – n (%)	788 (20.4)	611 (18.5)	77 (30.4)	140 (28.5)	77 (31.0)
≥70 – n (%)	334 (8.6)	241 (7.3)	57 (22.5)	116 (23.6)	52 (21.0)
Charlson Comorbidity Index – n (%)					
CCI = 0	2747 (71.0)	2395 (72.7)	140 (55.3)	263 (53.0)	140 (56.5)
CCI = 1	718 (18.6)	587 (17.8)	60 (23.7)	133 (26.8)	58 (23.4)
CCI ≥ 2	404 (10.4)	314 (9.5)	53 (20.9)	100 (20.2)	50 (20.2)
Myocardial infarction or congestive heart failure – n (%)	185 (4.8)	136 (4.1)	32 (12.6)	55 (11.1)	29 (11.7)
QT-prolonging drugs – n (%)	1518 (39.2)	1248 (37.9)	110 (43.5)	213 (42.9)	109 (44.0)
ECG measurements					
Heart rate (median, IQR)	85 (73-99)	87 (74-101)	76 (65-84)	76 (65-87)	76 (65-85)
QTc ≥500 ms - n (%)	27 (0.7)	-	27 (10.7)	-	27 (10.9)
Any diagnose of poisoning – n (%)	2676 (69.2)	2282 (69.2)	153 (60.5)	310 (62.5)	151 (60.9)
Group of poisoning – n (%)					
1.Analgesics and drugs of abuse	397 (14.8)	333 (14.6)	21 (13.7)	41 (13.2)	21 (13.9)
2.Psychotropic drugs and drugs affecting the central nervous system	805 (30.1)	695 (30.5)	49 (32.0)	103 (33.2)	49 (32.5)
3.Organic and chemical substances, non-medical	502 (18.8)	437 (19.1)	24 (15.7)	50 (16.1)	24 (15.9)
4.Others	470 (17.6)	392 (17.2)	30 (19.6)	54 (17.4)	29 (19.2)
5.Multidrug	502 (18.8)	425 (18.6)	29 (19.0)	62 (20.0)	28 (18.5)
Clinics – n (%)					
The University Hospital Skåne, Lund	1794 (46.4)	1539 (46.7)	125 (49.4)	247 (49.8)	124 (50.0)
Odense University Hospital	501 (12.9)	419 (12.7)	28 (11.1)	50 (10.1)	28 (11.3)
Helsingborg Hospital	1372 (35.5)	1176 (35.7)	81 (32.0)	170 (34.3)	79 (31.9)
Hospital of South West Jutland	202 (5.2)	162 (4.9)	19 (7.5)	29 (5.8)	17 (6.9)

Abbreviations: CCI, Charlson Comorbidity Index; IQR, interquartile range.
*In the total cohort patients with a near-overlapping QTc interval (440-449 ms men, 440-459 ms women) are included (n =320).

In addition, prescription of QT prolonging drugs was more frequent in the group with a prolonged QTc interval. Among the included patients, 6.5% (95% CI, 5.9-7.4) had QTc prolongation, while the prevalence of severe QTc prolongation (≥500 ms) was 0.7% (95% CI, 0.5-1.0). The prevalence of QTc prolongation in relation to specific groups of poisoning varied within the range 4.8-6.2%, with the highest prevalence in the group categorized as “others” (6.2%; 95% CI, 4.8-8.7) (Table 2).

Table 2: QTc prolongation in relation to poisoning groups

	Analgesics and drugs of abuse	Psychotropic drugs including drugs affecting the central nervous system	Chemical and biological substances, non-medical	Others	Multidrug
ICD-10 codes or definition	T39-T40, F110, F120, F140, F150, F160	T42-T44, F130, F190	T51-T65, F100, F170, F180	T36-T38, T41, T45-T50	≥2 of the described poisoning groups
N	397	805	502	470	502
QTc prolongation – n (%, CI 95%) ≥450 ms (men) ≥460 ms (women)	21 (5.3%; 3.3-8.0)	49 (6.1%; 4.5-8.0)	24 (4.8%; 3.1-7.0)	29 (6.2%; 4.2-8.7)	28 (5.6%; 3.7-8.0)

Abbreviation: CI, confidence interval.

Prognosis

Overall, the 30-day risk of all-cause mortality or cardiac arrest was 0.8% (95% CI, 0.6-1.2, n=32). Among individuals with QTc prolongation (n= 253), death within 30 days after contact to the ED occurred in 7 patients, whereas one patient suffered from cardiac arrest. Among those with a normal QTc interval (n=3616), we found 24 events during the follow-up period. The absolute risk of event within 30 days was 3.2% (95% CI, 1.4-6.1) and 0.7% (95% CI, 0.5-1.0) for patients with and without QTc prolongation, respectively.

The propensity score analysis included 248 patients with a QTc of ≥450 ms (men) or ≥460 ms (women) matched with 496 patients with a QTc interval <440 ms. Acceptable balance of baseline variables was achieved (Table 1). QTc prolongation was associated with a HR of 3.6 (95% CI, 1.0-12.2) for 30-day all-cause mortality or cardiac arrest (Table 3 and Figure 2).

Table 3: Risk assessment in the study population

Propensity score matched cohort	n	Events (No.)	HR** (95% CI)
Suspected poisoning			
Normal QTc interval <440 ms	496	n<5	1.0 (ref)
QTc prolongation ≥450 ms, men ≥460 ms, women	248	8	3.6 (1.0-12.2)
Diagnose of poisoning*			
Normal QTc interval <440 ms	310	n<5	1.0 (ref)
QTc prolongation ≥450 ms, men ≥460 ms, women	151	6	10.5 (1.2-90.0)

Abbreviations: CI, confidence interval; HR, hazard ratio. If the number of events in the analysis was less than 5 (marked by n<5), the number of patients in the strata is not shown.

*Patient who arrived with suspected poisoning and had a discharge diagnose of poisoning.

**Cox regression calculated after 1:2 propensity score matching comparing patients with QTc prolongation to patients without QTc prolongation. In this population, patients with near-overlapping ranges of the QTc interval were excluded (QTc 440-449 ms, men and 440-459 ms, women).

Subgroups and sensitivity analyses

Our results from the subgroup analysis are outlined in Appendix D. When restricting to those who also received a discharge diagnose of poisoning, we found an overall 30-day risk of 0.7% (95% CI, 0.4-1.1) and QTc prolongation yielded an overall HR of 10.5 (95% CI, 1.2-90.0). When we corrected the QT interval with the Bazett formula a total of 1112 patients had QTc prolongation (28.7%), which was associated with a HR of 1.0 (95% CI, 0.2-5.5).

DISCUSSION

In this transnational cohort of patients with suspected poisoning arriving to the ED, QTc prolongation was common (6.5%). A prolonged QTc interval was associated with a three-fold increased risk of 30-day all-cause mortality or cardiac arrest and an absolute risk of 3.2%.

This study has several strengths. First, this was a multicenter cohort study with data from two Swedish and two Danish EDs which ensured a broad representability. Use of personal identification numbers in all contacts to the hospital system in Sweden and Denmark provide the possibility to follow individual patients in and out of hospital and loss of follow-up or unmeasured registration of death did not occur. [17-22] In addition, we implemented several confounders in our propensity score model, and thus managed to control for these despite a low event-rate. We included patients who were suspected for being poisoned on arrival to the ED. These patients do – in contrast to patients identified by their discharge diagnosis – represent the clinical situation at the door in the ED. At this point, the doctors have to decide whether or not to observe the patients using telemetry.

This study also has several limitations. First of all, the design was an observational design. The ECG measures were all automatic readouts, and we did not manually validate the length of the QT intervals. However, this method has been validated in a previous Danish study using the same technique, which showed a good overall agreement between manual QTc interval and the digital record of the QTc interval with a mean difference of 1.3 ms.[8] Further, we did not exclude ECGs with diagnoses complicating QTc measuring, e.g. atrial fibrillation. We did not have information regarding previous ECGs, and we do not know if some patients had a previous ECG with QTc prolongation before arrival with suspected poisoning. The dose of drug or substance was unknown, and we were ignorant of the timing of the ECG recording in relation to peak drug concentration. The poisonings were not confirmed by blood samples or by urine tests, but were extracted from predefined ICD-10 codes.

The small number of events was a limitation in its own and did not allow for meaningful subgroup analysis. As cardiac arrest was identified based on hospital registration an eventually event of unregistered cardiac arrest, where the patient survived, is not included as an event. The number of these events is believed to be small as registration of cardiac arrest is mandatory in both the Swedish and Danish health care system. With a small number of events any miscounting of events would lead to considerable change in risk estimates. If we have overlooked one event of cardiac arrest who survived in the group of patients with QTc prolongation it would increase the absolute risk from 3.2% to 3.6%, while the risk of event in the entire study population would increase from 0.8% to 0.9%.

The event-rate in our cohort (0.8%) is in accordance with previous studies of poisoned patients (0.5-1.2%).[16,33,34] In contrast, the prevalence of QTc prolongation is substantially lower (6.5%) than in a previous study of unselected ED patients (35%).[35] This is probably due to the choice of QT correcting formula. If the Bazett formula had been chosen for main analysis, the prevalence of QTc prolongation in our study population would have been 28,7%. It is of broad consensus that the more widely used Bazett formula tends to overcorrect at heart rates at 80-90 beats per minute and above resulting in a higher prevalence of QTc prolongation.[32,36] As a high percentage of acute patients have tachycardia at arrival, this probably explains most of the difference between the occurrence of QTc prolongation in our study and in the study of unselected ED patients. The Framingham formula used in our study is considered superior compared with the more widely used Bazett formula.[36]

The clinical impact of our findings is the difference in risk of all-cause mortality and cardiac arrest within 30 days in respect to QTc prolongation. We found an absolute risk of 0.7% in patients with suspected poisoning without QTc prolongation, whereas patients with a prolonged QTc interval have an absolute risk of 3.2%, which translates into a HR of 3.6 (95% CI, 1.0-12.2). In the general population, a meta-analysis reported a pooled relative risk of 1.35 (95% CI, 1.24-1.46) for long-term mortality in patients with QTc prolongation.[7] A recent study including all patients who had an ECG recorded at the hospital for any reason reported QTc prolongation to be associated with a HR of 7.3 (95% CI, 4.10-13.05) for 30-day mortality.[36] Combined, these studies support the hypothesis that patients with a prolonged QTc are at increased risk. Whether or not this is directly linked to the increased QTc interval or due to other risk factors associated with a prolonged QTc remains unknown.

As demonstrated in our cohort the prevalence of QTc prolongation is strongly associated to the correction formula. Further, the difference between the HR calculated in the main analysis using Framingham (HR 3.6; CI 95%, 1.0-12.2) versus the sensitivity analysis using Bazett (HR 1.0; 95% CI, 0.2-5.5) is remarkable. We suspect that using the Bazett formula dilutes the association by including more patients at low risk as a result of overcorrection.

Despite the use of a propensity score model adjusting for several covariates, we cannot exclude residual confounding. From a clinical point of view, this means that the patients with a prolonged QTc probably need special care and attention. However, the needed care is not necessarily limited to telemetry and increased cardiac awareness. Of note, a ventricular arrhythmia with fatal outcome caused by drug-induced QTc prolongation, would be expected to happen within a relatively short time-interval after exposure. This was not the case in our study with the first event occurring three days after contact (see Figure 2). In addition, a QTc interval threshold for identification of patients in need of cardiac telemetry is not well-established. Unfortunately, our cohort was too small to do further subdivisions of the QTc interval.

Ventricular arrhythmias, especially torsades de pointes, are feared consequences of QT prolongation and may be the cause of death in some poisonings.[37,38] However, as torsades de pointes is a rare condition,[37,38] it is unlikely to have influenced our results.

In this cohort of patients with suspected poisoning 69.2% received a discharge diagnose of poisoning. This is in contrast to results from a previous Danish study, which found an agreement of 79% for suspected poisoning on arrival and a discharge diagnose of poisoning.[17] In our cohort, only those who had an ECG recorded were included, and several common poisonings, e.g. alcohol intoxication, are usually not followed by ECG recording.

QTc prolongation was most frequent in the group of poisoning labeled “others” (Table 2). In this group, the ICD-10 code T50.9 for unspecific poisonings was given to the majority of the patients. These patients might have been too sick to tell about their poisoning or perhaps denied to do so. This reflects a common clinical problem in the ED, and indicates that a specific poisoning diagnosis can be difficult to establish. Further, lack of precision in coding procedure may contribute to unspecific diagnoses.

In conclusion, we found QTc prolongation in a mixed population of patients with suspected poisoning in the emergency department of two Swedish and two Danish hospitals to be associated with a three-fold risk of 30-day all-cause mortality or cardiac arrest and an absolute risk of 3.2%.

Founding

This study was funded by an independent grant from The Research Foundation of Odense University Hospital. The funding sources had no role in the design of the study, data analysis or interpretation of the results.

Competing interests

ATL was supported by an unrestricted grant to the University of Southern Denmark from TrygFoundation. All other authors declare no conflicts of interest.

Author contributions

CSH designed the study, interpreted the results and drafted the paper. AP analyzed the data. CSH, AP, ATL, HKJ, UE, MB, and JLF conceived the study. ATL, AP and HKJ provided statistical advice and advice on the study design. AP, ATL, HKJ, UE, MB, and JLF critically reviewed the paper, assisted with interpretation of the results, and have approved the final edition. CSH takes responsibility for the final paper.

Data sharing statement

Due to Danish law regarding personal data we are not allowed to share data in public dataset. However, we welcome every researcher who wants to repeat the analysis or do new analysis in the dataset. Please contact professor Annmarie Lassen (Annmarie.Lassen@rsyd.dk) and she will help the researcher to get access to the data.

REFERENCES

1. Carter-Storch R, Olsen UF, Mogensen CB. Admissions to emergency department may be classified into specific complaint categories. *Dan Med J.* 2014;61(3):A4802.
2. Safwenberg U, Terént A, Lind L. Differences in Long-term Mortality for Different Emergency Department Presenting Complaints. *Acad Emerg Med.* 2008;15(1):9-16.
3. Woosley RL, Romero KA. QTdrugs List. AZCERT, Inc. https://www.crediblemeds.org/new-drug-list/. Updated August 10, 2016. Accessed December 17, 2015.
4. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 1999;20(4):278-284.
5. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol.* 2006;47(2):362-367.
6. Robbins J, Nelson JC, Rautaharju PM, et al. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. *Am J Med.* 2003;115(9):689-694.
7. Zhang Y, Post WS, Blasco-Colmenares E, et al. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology.* 2011;22(5):660-670.
8. Nielsen JB, Graff C, Rasmussen PV, et al. Risk prediction of cardiovascular death based on the QTc interval: evaluating age and gender differences in a large primary care population. *Eur Heart J.* 2014;35(20):1335-1344.
9. Panoulas VF, Toms TE, Douglas KM, et al. Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: an association driven by high inflammatory burden. *Rheumatology (Oxford).* 2014;53(1):131-137.
10. Straus SM, Sturkenboom MC, Bleumink GS, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J.* 2005;26(19):2007-2012.
11. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med.* 2009;360(3):225-235.
12. Ray WA, Meredith S, Thapa PB, et al. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther.* 2004;75(3):234-241.
13. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366(20):1881-1890.
14. Drew BJ, Califf RM, Funk M, et al. Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. *Circulation.* 2004;110(17):2721-2746.
15. Manini AF, Nelson LS, Skolnick AH, et al. Electrocardiographic predictors of adverse cardiovascular events in suspected poisoning. *J Med Toxicol.* 2010;6(2):106-115.
16. Manini AF, Hoffman RS, Stimmel B, et al. Clinical risk factors for in-hospital adverse cardiovascular events after acute drug overdose. *Acad Emerg Med.* 2015;22(5):499-507.
17. Norgaard B, Mogensen CB, Teglbjaerg LS, et al. Diagnostic packages can be assigned accurately in emergency departments. A multi-centre cohort study. *Dan Med J.* 2016;63(6):A5240.
18. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015;7:449-490.
19. Pottegard A, Schmidt SA, Wallach-Kildemoes H, et al. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol.* 2016.
20. Astrand B, Hovstadius B, Antonov K, et al. The Swedish National Pharmacy Register. *Stud Health Technol Inform.* 2007;129(Pt 1):345-349.
21. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* 2014;29(8):541-549.

22. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;24(11):659-667.
23. *Marquette™ 12SL™ ECG Analysis Program. Physician's Guide. 2056246-002 Revision B.* Milwaukee, WI: GE Healthcare; 13 July 2015.
24. *Läkarhandbok för Phillips DXL-algoritm för EKG. Publikationsnummer 453564149891.* Andover, MA: Phillips Medical Systems; 1 June 2009.
25. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol.* 1992;70(7):797-801.
26. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation.* 2009;119(10):e241-250.
27. Sturmer T, Joshi M, Glynn RJ, et al. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. *J Clin Epidemiol.* 2006;59(5):437-447.
28. Rassen JA, Shelat AA, Myers J, et al. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl 2:69-80.
29. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
30. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-1139.
31. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat.* 2011;10(2):150-161.
32. C. BH. An analysis of time-relations of electrocardiograms. *Heart.* 1920;7:353-370.
33. Manini AF, Nelson LS, Stimmel B, et al. Incidence of adverse cardiovascular events in adults following drug overdose. *Acad Emerg Med.* 2012;19(7):843-849.
34. Gunnell D, Ho D, Murray V. Medical management of deliberate drug overdose: a neglected area for suicide prevention? *Emerg Med J.* 2004;21(1):35-38.
35. Seftchick MW, Adler PH, Hsieh M, et al. The prevalence and factors associated with QTc prolongation among emergency department patients. *Ann Emerg Med.* 2009;54(6):763-768.
36. Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? *Journal of the American Heart Association.* 2016;5(6):e003264.
37. Al-Abri SA, Woodburn C, Olson KR, et al. Ventricular dysrhythmias associated with poisoning and drug overdose: a 10-year review of statewide poison control center data from California. *Am J Cardiovasc Drugs.* 2015;15(1):43-50.
38. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003;89(11):1363-1372.

Legends for figures

Figure 1: Flowchart of the study population

Figure 2: Kaplan Meier failure estimate

Abbreviations: QTclong = 0, patients without QTc prolongation; QTclong = 1, patients with QTc prolongation.

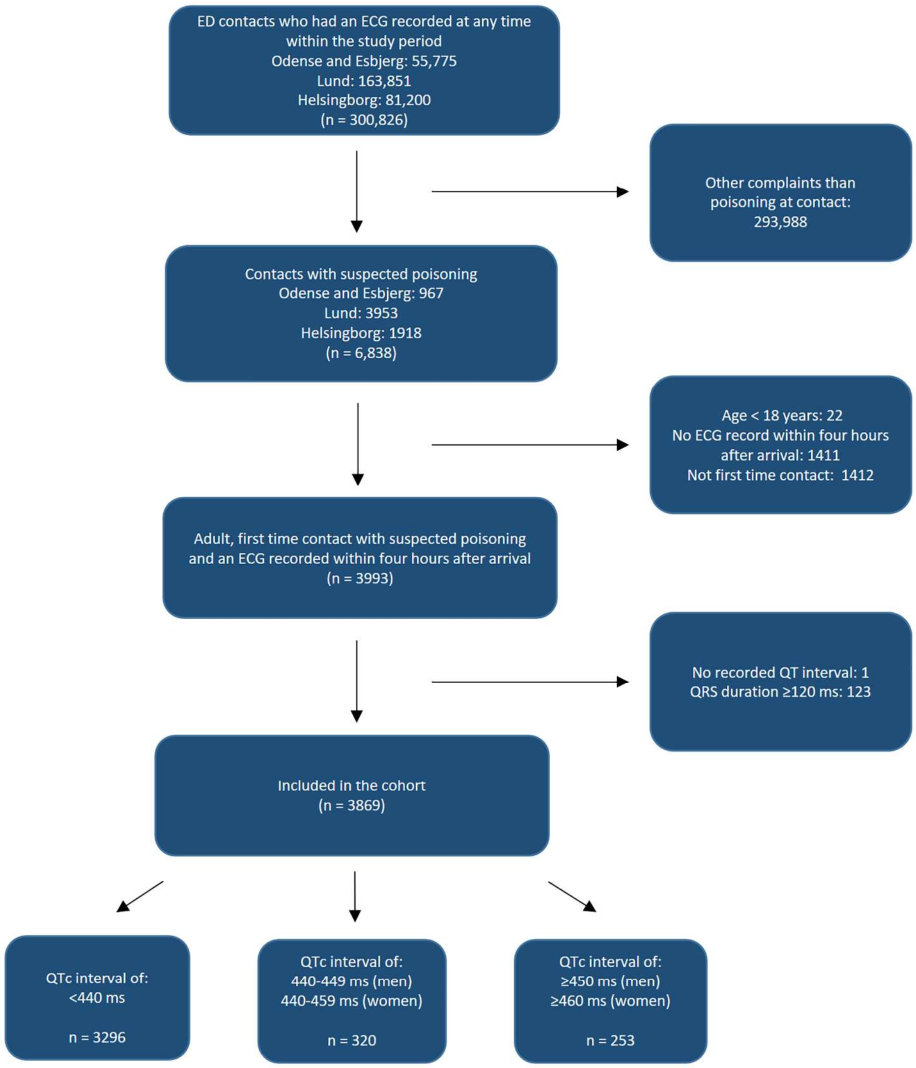

Figure 1: Flowchart of the study population

203x220mm (300 x 300 DPI)

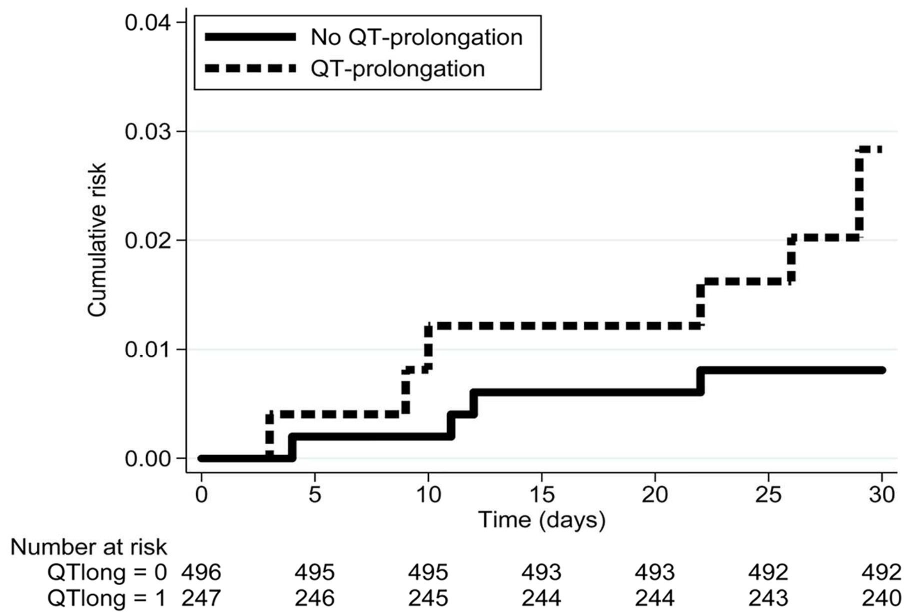

Figure 2: Kaplan Meier failure estimate
Abbreviations: QTclong = 0, patients without QTc prolongation; QTclong = 1, patients with QTc prolongation.

203x144mm (300 x 300 DPI)

APPENDIX

Appendix A – Data sources

In the logistic system in the EDs of the Region of Southern Denmark and the Region of Skåne information regarding triage and presumed diagnoses are shared among the health care personal. The system also provides information on time of arrival to the ED as well as time of discharge. At arrival all patients are registered by main reason for contact. Lund and Helsingborg have 43 somatic contact possibilities, Odense and Esbjerg have 40 contact possibilities. We used these systems to identify patients with suspected poisoning.
From the electronic central ECG databases at the Region of Southern Denmark and the Region of Skåne all ECGs measures were extracted. These databases contain information of all ECGs recorded in any hospital in the respective region.

The Danish National Patient Register was established in 1977. Since 1994 diagnostic information has been recorded in accordance with ICD-10. The content includes information regarding discharge diagnoses from which comorbidities were derived. In Sweden, all health care consultations are recorded in the respective region databases. From the Skåne Healthcare Register, we retrieved information corresponding to information from the Danish National Patient Register. In these regional databases diagnoses from both the primary and secondary health care system are available. Charlson Comorbidity Index was calculated based on data extracted for a 10 year-period ending on the day of contact in the Danish data. From the Swedish database, Charlson Comorbidity Index was calculated for a 2-year period ending on the day of contact to the ED.

The Swedish National Pharmacy Register contains data on all prescriptions dispensed at pharmacies since 2005. Besides date of dispensing, name, amount, and dose of the redeemed medication are accessible from this register. The Danish National Prescription Registry provides similar information of individual-level prescription of medication since 1995. Information of redeemed prescription of QT prolonging drugs (see Appendix c.5) within 90 days before contact was obtained through these registers.

The Danish Civil Registration System contains data regarding birth, emigration, and vital status for the entire populations. Information regarding vital status in Sweden was retrieved from the Swedish population registry. The Danish Civil Registration System was established in 1968, and by law all Danish residents have a unique civil registration number of ten digits. Since 1967, all Swedish residences are assigned a ten-digit personal identity number. These unique numbers allow complete and accurate linkage between registries on an individual level.

Appendix B – Supplementary methods

ECG measurements

All ECGs were recorded and stored either in MUSE® Cardiology Information System (GE Healthcare), or by Philips Diagnostic ECG (Philips). All ECGs in our analysis were 12 lead ECGs. ECGs recorded in MUSE were later processed using the Marquette 12SL algorithm, which calculate the QTc interval using the Bazett Formula, the Fridericia Formula, and the Framingham Formula. In MUSE, the QT interval is measured as a median value from the 12 leads. ECG recorded by Philips were analyzed by the DXL-algorithm. In this algorithm, the QT interval is measured as a median value from reliable leads. A lead is defined as reliable if little variation in beat-to-beat variation. Philips provided QTc intervals corrected by the Bazett Formula and the Fridericia Formula. To correct for heart rate, we chose the Framingham Formula ($QTc_{Framingham}$ =QT + 0.154 (1-RR)). Because Philips DXL-algorithm does not routinely correct the QT interval using the Framingham Formula, we calculated the $QTc_{Framingham}$ ourselves. As we did not include RR intervals in our analysis, the formula was used in another edition than the original formula. Therefore, we used following formula for correction in ECGs recorded by Philips: $QTc_{Framingham}$ = QT + 154 (1-60/heart rate). The QRS duration was measured as a median value in both algorithms.

The Marquette 12SL algorithm defines onsets as the earliest deflection in any lead, and offsets as the latest deflection in any lead. The QT interval is measured from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead. Similarly, the QRS duration was measured from the earliest onset in any lead to the latest deflection in any lead. The Philips DXL-algorithm first identifies waveform component and measures every beat in each lead individually. After the approximate waveform locations are known, onsets and offsets are defined. Once the onsets and offsets are known, duration of intervals are calculated.

In both Denmark and Sweden ECG recording is performed by well-educated heath care personals instructed only to accept ECGs of satisfying quality. Otherwise it is considered a routine to record another ECG. If multiple ECGs were recorded in a single individual, the first ECG recorded within 4 hours after arrival was included in the analysis.

Appendix C – Codes and definitions

C.1

Codes for cardiac arrest and codes used in identifying patients with cardiac arrest	
ICD-10 codes	DI46: Cardiac arrest DI46.0: Cardiac arrest with successful recitation DI46.1: Sudden cardiac death DI46.9: Cardiac arrest unspecified
SKS codes*	**Administrative codes** AVAA07: Sudden cardiac arrest AVAA06: Sudden cardiac arrest **Procedure codes** ZZ0401: Standby for cardiac arrest **Treatment codes** BFFA6: Chest compressions BFFA60: External chest compressions BFFA60A: External chest compressions by use of mechanical chest compressions
KVÅ-codes**	DF012: Chest compressions DF017: Mechanical chest compressions DF028: Cardiopulmonary resuscitation

*SKS = Sundhedsvæsenets klassifikations system, available on http://medinfo.dk/sks/brows.php, Danish codes.
**KVÅ= Klassifikation av vårdåtgärder, available on http://www.socialstyrelsen.se/klassificeringochkoder/atgardskoderkva, Swedish codes.

C.2

Poisoning divided into groups by use of ICD-10 codes	
Analgesics and drugs of abuse	T39*-T40*, F110*, F120*, F140*, F150*, F160*
Psychotropic drugs and drugs affecting the central nervous system	T42*-T44*, F130*, F190*
Organic and chemical substances, non-medical substances	T51*-T65*, F100*, F170*, F180*
Others	T36*-T38*, T41*, T45*-T50*
Multidrug	≥2 of the above mentioned poisoning groups

C.3

Charlson Comorbidity Index*		
Condition	**Assigned weight**	**ICD-10 codes**
Peripheral vascular disease	1	I70.x, I71x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	1	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	1	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Rheumatic disease	1	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	1	K25.x-K28.x
Mild liver disease	1	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	1	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Hemiplegia or paraplegia	2	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
Renal disease	2	I12.0, I13.1, N03.2-N03.7, N05.2- N05.7, N18.x, N19.x, N25.0, Z49.0- Z49.2, Z94.0, Z99.2
Diabetes with chronic complications	2	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2- E13.5, E13.7, E14.2-E14.5, E14.7
Cancer	2	C00.x-C26.x, C30.x-C34.x, C37.x- C41.x, C43.x, C45.x-C58.x, C60.x- C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Metastatic cancer	3	C77.x-C80.x
Moderate or severe liver disease	3	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
AIDS/HIV**	6	B20.x-B22.x, B24.x

*Diagnostic codes for myocardial infarction and heart failure are not included in the index, but are included in this study as covariates.

** AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus

C.4

Variables from Charlson Comorbidity Index, included separately in the analysis	
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0

C.5

List of drugs associated with QT prolongation and risk of TdP*	
Drug category	**ATC-codes****
Alimentary tract and metabolism	Domperidone (A03FA03), Granisetron (A04AA02), Metoclopramide (A03FA01), Ondansetron (A04AA01), Pantoprazole (A02BC02)
Cardiovascular system	Amiodarone (C01BD01), Dronedarone (C01BD07), Flecainide (C01BC04), Furosemide (C03CA01, C03EB01), Hydrochlorothiazide (C03EA01, C09DA01, C09DA06, C09DA04, C09BA02), Indapamide (C03BA11), Isradipine (C08CA03), Ivabradine (C01EB17), Sotalol (C07AA07)
Genito urinary system and sex hormones	Alfuzosin (G04CA01), Mifepristone (G03XB01), Mirabegron (G04BD12), Solifenacin (G04BD08, G04CA53), Tolterodine (G04BD07), Vardenafil (G04BE09)

Systemic hormonal preparations, excl. sex hormones and insulins	Oxytocin (H01BB02), Pasireotide (H01CB05)
Anti-infectives for systemic use	Atazanavir (J05AR15), Azithromycin (J01FA10), Bedaquiline (J04AK05), Ciprofloxacin (J01MA02), Clarithromycin (J01FA09), Erythromycin (J01FA01), Fluconazole (J02AC01), Foscarnet (J05AD), Itraconazole (J02AC02), Ketoconazole (J02AB02), Metronidazole (J01XD01), Moxifloxacin (J01MA14), Posaconazole (J02AC04), Rilpivirine (J05AG05), Ritonavir (J05AE03), Roxithromycin (J01FA06), Saquinavir (J05AE01), Voriconazole (J02AC03)
Antineoplastic and immunomodulatory agents	Anagrelide (L01XX35), Bortezomib (L01XX32), Bosutinib (L01XE14), Ceritinib (L01XE28), Crizotinib (L01XE16), Dabrafenib (L01XE23), Dasatinib (L01XE06), Degarelix (L02BX02), Eribulin mesylate (L01XX41), Fingolimod (L04AA27), Lapatinib (L01XE07), Leuprolide (L02AE02), Nilotinib (L01XE08), Oxaliplatin (L01XA03), Panobinostat (L01XX42), Pazopanib (L01XE11), Sorafenib (L01XE05), Sunitinib (L01XE04), Tacrolimus (L04AD02), Tamoxifen (L02BA01), Vandetanib (L01XE12), Vemurafenib (L01XE15)
Musculo-skeletal system	Tizanidine (M03BX02)
Nervous system	Amantadine (N04BB01), Amisulpride (N05AL05), Amitriptyline (N06AA09), Apomorphine (N04BC07), Aripiprazole (N05AX12), Asenapine (N05AH05), Atomoxetine (N06BA09), Citalopram (N06AB04), Clomipramine (N06AA04), Clozapine (N05AH02), Dexmedetomidin (N05CM18), Doxepin (N06AA12), Droperidol (N05AD08), Escitalopram (N06AB10), Fluoxetine (N06AB03), Galantamine (N06DA04), Haloperidol (N05AD01), Hydroxyzine (N05BB01), Imipramine (N06AA02), Levomepromazine (N05AA02), Lithium (N05AN01), Methadone (N07BC02), Mirtazapine (N06AX11), Nortriptyline (N06AA10), Olanzapine (N05AH03), Paliperidone (N05AX13), Paroxetine (N06AB05), Pimozide (N05AG02), Pipamperone (N05AD05), Propofol (N01AX10), Quetiapine (N05H04), Risperidone (N05AX08), Sertindole (N05AE03), Sertraline (N06AB06), Sevoflurane (N01AB08), Sulpiride (N05AL01), Tetrabenazine (N07XX06), Venlafaxine (N06AX16), Ziprasidone (N05AE04)
Antiparasitic products, insecticides and repellents	Chloroquine (P01BC02), Hydroxychloroquine (P01BA02), Metronidazole (P01AB01), Pentamidine (P01CX01), Quinine sulfate (P01BC01)
Respiratory system	Diphenhydramine (R06AA02), Promethazine (R06AD02)
Various	Perflutren lipid microspheres (V08DA01)

*From QTDrug list, https://crediblemeds.org/, version December 17, 2015. Only drugs available in Denmark are included at our list. The list includes drugs with known risk of TdP, possible risk of TdP, and conditional risk of TdP.
**ATC = Anatomical Therapeutic Chemical

Appendix D – Supplementary results

Results from stratified analysis. Although further strata than shown in this table were preplanned (e.g. stratification on all poisoning groups and age), we only stratified when possible due to a small number of events.

	QTc prolongation QTc ≥450 ms, men QTc ≥460 ms, women	Normal QTc interval <440 ms, men and women	HR* (95% CI)
	Events (n)**	Events (n)**	
Suspected poisoning			
Total	8 (248)	n<5 (496)	3.6 (1.0-12.2)
Male	n<5	n<5	2.7 (0.5-16.3)
Female	n<5	n<5	4.4 (0.8-24.3)
Age ≥50 years	6 (131)	n<5	2.7 (0.7-9.9)
Odense or Esbjerg	n<5	n<5	5.8 (0.6-57.4)
Lund	n<5	n<5	1.7 (0.2-12.2)
Helsingborg	n<5	n<5	4.4 (0.4-49.2)
Confirmed poisoning			
Total	6 (151)	n<5	10.5 (1.2-90.0)
Psychotropic drugs	n<5	n<5	2.0 (0.1-32.5)

Abbreviations: HR; hazard ratio, CI; confidence interval.
*Hazard ratio from Cox regression.
**If the number of events in the analysis was less than 5 (marked by n<5), the number of patients in the strata is not shown.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1 and 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 3**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 3-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4 and 5** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **Page 5** (As we did a propensity score analysis the number of exposed and unexposed are outlined in the results because it cannot be provided before the analysis) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4, 5, and Appendix B and C**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4 and Appendix A, B, and C**
Bias	9	Describe any efforts to address potential sources of bias **Page 6**
Study size	10	Explain how the study size was arrived at **Page 4 and figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,

		describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5 and 6**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5 and 6**
		(*c*) Explain how missing data were addressed **No missing data.**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **No loss to follow-up.** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 6**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 6**
		(b) Give reasons for non-participation at each stage **Page 6**
		(c) Consider use of a flow diagram **Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 6 and 7, including table 1**
		(b) Indicate number of participants with missing data for each variable of interest **None missing**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 8**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 8 and table 3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7 and 8 including table 3**
		(*b*) Report category boundaries when continuous variables were categorized **Page 5**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Page 8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses The prevalence of QTc prolongation in relation to specific subgroups: **page 7 and table 2.** **Appendix D** includes a stratified analysis. Sensitivity analysis: **page 8 and 9.**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 9 and 10.**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 10 and 11.**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 9 and 10.**

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 12**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The association between QTc prolongation and mortality in patients with suspected poisoning in the emergency department – a transnational propensity score matched cohort study

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Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	EPIDEMIOLOGY, CARDIOLOGY, TOXICOLOGY

The association between QTc prolongation and mortality in patients with suspected poisoning in the emergency department – a transnational propensity score matched cohort study

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ABSTRACT

OBJECTIVES: Poisoning is a frequent cause of admission to the emergency department (ED), and may involve drugs known to prolong the QT interval. The aims of this study were to describe the prevalence of QTc prolongation among ED patients with suspected poisoning and to calculate the absolute and relative risk of mortality or cardiac arrest associated with a prolonged QTc interval.

METHODS: We performed a register-based cohort study, including all adult first time contacts with suspected poisoning to the ED of two Swedish hospitals (January 2010 to December 2014) and two Danish hospitals (March 2013 to April 2014). We used propensity score matching to calculate hazard ratios (HR) for all-cause mortality or cardiac arrest (combined endpoint) within 30 days after contact comparing patients with a prolonged QTc interval (≥450 ms men, ≥460 ms women) with patients with a QTc interval of <440 ms.

RESULTS: Among all first-time contacts with suspected poisoning that had an ECG recorded within four hours after arrival (n = 3869), QTc prolongation occurred in 6.5%. The overall mortality after a 30-day follow-up period was 0.8% (95% CI, 0.6-1.2), with an absolute risk of mortality or cardiac arrest in patients with QTc prolongation of 3.2% (95% CI, 1.4-6.1). A prolonged QTc interval on arrival was associated with a HR of 3.6 (95% CI, 1.0-12.2).

CONCLUSION: In the ED, a prolonged QTc interval in patients arriving with suspected poisoning seems to be associated with a three-fold increased risk of 30-day all-cause mortality or cardiac arrest.

Strengths and limitations of the study

Patients were included from four different hospitals – two Swedish and two Danish.

Propensity score matching was used to adjust for several confounders.

Subgroups analysis was not possible due to a small number of events.

The included ECGs were all automatic readouts and the length of the QT interval was not confirmed manually.

INTRODUCTION

Poisoning is a frequent cause of admission to the emergency department (ED),[1,2] and involves a variety of different drugs and substances. A wide range of drugs have been linked to QTc prolongation,[3] which has been associated with all-cause-mortality, cardiovascular death, and sudden cardiac death.[4-9] As an increased risk of mortality has been documented in patients treated with potential QTc prolonging drugs,[10-13] one may hypothesize that the risk is even higher among poisoned patients. Therefore, cardiac monitoring is recommended in patients poisoned by potentially proarrhythmic agents and drugs that can lead to torsades de pointes.[14]

Only few studies have investigated the relationship between QTc prolongation and adverse outcomes in a population of undifferentiated poisoned patients.[15,16] The absolute and relative risk of mortality and cardiac arrest associated to QTc prolongation in poisoned patients remains unknown. Therefore, we aimed to: (1) describe the prevalence of QTc prolongation found among patients with suspected poisoning in the emergency department; (2) to investigate if QTc prolongation is associated with an increased risk of mortality or cardiac arrest within 30 days after arrival to the emergency department.

MATERIALS AND METHODS

Study design and setting

This is a register-based cohort study. The study is based on ED data from January 1 2010 to December 31 2014 from two Swedish hospitals (Skåne University Hospital, Lund and Helsingborg Hospital) and from two Danish hospitals (Odense University Hospital and the Hospital of South West Jutland, Esbjerg) from March 1 2013 to April 30 2014. In both Denmark and Sweden, the healthcare systems are tax-funded and all residents have free access to healthcare. The University

Hospital Skåne has a contingency population of approximately 310,000, whereas Odense University Hospital covers a population of 290,000 people. The two regional hospitals have a contingency population of 250,000 people (Helsingborg), and 220,000 people (Esbjerg).

Selection of participants

We identified all adults (≥18 years), who arrived to the EDs with suspected poisoning. The contacts were eligible for the main analysis if they had a 12-lead ECG recorded within 4 hours after arrival. A missing QTc interval on the recorded ECG, or a QRS duration of ≥120 ms were both reasons for exclusion. Patients with multiple contacts were included only at their first contact with suspected poisoning within the study period. Information regarding identification of patients with suspected poisoning is outlined in Appendix A.

Data sources

In both Denmark and Sweden, all residents have a unique personal civil registration number, which allows cross-linkage at personal level between databases. We extracted data from several registries: The logistic systems in the ED at the Region of Southern Denmark[17] and Region of Skåne, the electronic central ECG databases at Region of Southern Denmark and Region of Skåne, the Danish National Patient Registry[18] and Region of Skåne Health care databases, the Danish National Prescription Registry,[19] the Swedish Pharmacy Registry,[20] and finally The Danish Civil Registration System[21] and the Swedish Population Register.[22] Further information regarding the data sources is provided in Appendix A.

ECG measurements and definitions

The QT interval was measured at the first ECG recorded after contact to the ED. All the QT intervals were calculated automatically as a median value and stored in either MUSE Cardiology Information System (GE Healthcare) or Philips Diagnostic ECG. The GE Marquette 12SL ECG Analysis Program provided QTc intervals for ECGs recoded in MUSE.[23] ECGs recorded by Phillips were analyzed by the DXL-algorithm.[24] Only QT intervals corrected for heart rate (QTc) was used in our analysis. For correction, we chose the Framingham Formula ($QTc_{Framingham}$ =QT + 0.154 (1-RR)).[25] Additional details about ECG measurements are outlined in Appendix B.

Exposure and outcome

Our primary outcome was a combined endpoint of all-cause mortality or cardiac arrest (defined in Appendix C.1) within 30 days from the day of arrival to the ED. All patients were followed for 30 days, including those transferred to another department. Patients who died in relation to cardiac arrest were classified as dead rather than cardiac arrests. The primary exposure was QTc prolongation, defined as a QTc of ≥450 ms for men and ≥460 ms for women.[26] Patients with a normal QTc length were defined as having a QTc interval of <450 ms (men) or <460 ms (women).

Analysis

The prevalence of QTc prolongation overall, and in relation to specific groups of poisoning was described in a cross-sectional description. In this description, we identified all patients with a discharge diagnosis of poisoning (International Classification of Diseases (ICD-10) codes T36*-T65*, F100*, F110*, F120*, F130*, F140*, F150*, F160*, F170*, F180* or F190* as a primary or secondary diagnosis). All patients, who had a discharge diagnosis of poisoning, were subdivided into five poisoning groups: 1. Analgesics and drugs of abuse, 2. Psychotropic drugs including drugs affecting the central nervous system, 3. Organic and chemical substances, non-medical, 4. Others, and 5. Multidrug (see Appendix C.2).

The association between QTc prolongation and all-cause mortality and cardiac arrest was evaluated using propensity score matching.[27,28] We calculated a propensity score for all included patients by use of logistic regression with QTc ≥450 ms (men) or ≥460 ms (women) as the outcome (binary outcome). Patients with a QTc interval between 440-449 ms (men) and 440-459 ms (women) were excluded in the model to avoid near-overlapping ranges. The following possible confounders were included in the propensity score model: sex, age, comorbidity (measured as Charlson Comorbidity Index[29,30]), history of myocardial infarction or congestive heart failure (Appendix C3. and C.4), prescription of QT prolonging drugs within 90 days (defined in Appendix C.5)[31], heart rate, and study center. We performed a 1:2 parallel balanced nearest neighbor matching without replacement and with a caliper of 0.05.[32] In the matched cohorts, 30-day mortality was modelled using Cox regression.

Statistics

The absolute risk of event in patients with suspected poisoning was calculated overall, for those with QTc prolongation and for those without QTc prolongation. In the propensity score matched cohort, the risk associated with QTc prolongation was estimated as hazard ratios (HR). We estimated 95% confidence intervals based on a binominal distribution. To illustrate the impact of QTc prolongation on 30-days all-cause mortality or cardiac arrest we generated a Kaplan Meier failure curve.

In a sensitivity analysis, we restricted the material to individuals who were both suspected of being poisoned on arrival and received a discharge diagnose of poisoning. The prevalence of QTc prolongation and the propensity score analyses were repeated using the Bazett formula for QT correction.[33]

Statistical analyses were performed using STATA version 14 (StataCorp LP, College Station, Texas). The study was approved by the Danish Data Protection Agency (No. 2008-58-0035, Journal nr. 15/21632) and The Danish Health Authority (No. 3-3013-1031). In consistency with Swedish law the study was approved by the Regional Ethics Committee in Lund and by Region Skåne.

Patient and public involvement

This was a study without contact to patients. All information was obtained through registers.

RESULTS

Characteristics of the study cohort

At the four hospitals, we identified a total of 6838 ED contacts with suspected poisoning. After exclusion of those aged <18 years (n=22), an ECG not recorded in an acceptable time-interval (n=1411), multiple contacts within the study period (n=1412), a missing QT interval (n=1), or QRS duration ≥120 ms (n=123) the final cohort comprised 3869 patients with suspected poisoning (48.0% men, median age 38) (Figure 1). Of these, 69.2% (n=2676) had a discharge diagnose of poisoning.

Patients with a prolonged QTc interval were older, had more comorbidity, and more commonly had a history of heart disease than those without QTc prolongation (Table 1).

Table 1: Baseline characteristics of the study population

	All*	Before propensity score matching		After propensity score matching	
		QTc <440 ms (men and women)	**Prolonged QTc** ≥450 ms (men) ≥460 ms (women)	**QTc** <440 ms (men and women)	**Prolonged QTc** ≥450 ms (men) ≥460 ms (women)
N	**3869**	**3296**	**253**	**496**	**248**
Sex Male (%)	1859 (48.0)	1634 (49.6)	121 (47.8)	229 (46.2)	119 (48.0)
Age (median, IQR)	38 (25-53)	36 (24-51)	52 (36-68)	53 (37-69)	51 (35-66)
18-50 – n (%)	2747 (71.0)	2444 (74.2)	119 (47.0)	236 (48.0)	119 (48.0)
51-69 – n (%)	788 (20.4)	611 (18.5)	77 (30.4)	140 (28.5)	77 (31.0)
≥70 – n (%)	334 (8.6)	241 (7.3)	57 (22.5)	116 (23.6)	52 (21.0)
Charlson Comorbidity Index – n (%)					
CCI = 0	2747 (71.0)	2395 (72.7)	140 (55.3)	263 (53.0)	140 (56.5)
CCI = 1	718 (18.6)	587 (17.8)	60 (23.7)	133 (26.8)	58 (23.4)
CCI ≥ 2	404 (10.4)	314 (9.5)	53 (20.9)	100 (20.2)	50 (20.2)
Myocardial infarction or congestive heart failure – n (%)	185 (4.8)	136 (4.1)	32 (12.6)	55 (11.1)	29 (11.7)
QT-prolonging drugs – n (%)	1518 (39.2)	1248 (37.9)	110 (43.5)	213 (42.9)	109 (44.0)
ECG measurements					
Heart rate (median, IQR)	85 (73-99)	87 (74-101)	76 (65-84)	76 (65-87)	76 (65-85)
QTc ≥500 ms - n (%)	27 (0.7)	-	27 (10.7)	-	27 (10.9)
Any diagnose of poisoning – n (%)	2676 (69.2)	2282 (69.2)	153 (60.5)	310 (62.5)	151 (60.9)
Group of poisoning – n (%)					
1.Analgesics and drugs of abuse	397 (14.8)	333 (14.6)	21 (13.7)	41 (13.2)	21 (13.9)
2.Psychotropic drugs and drugs affecting the central nervous system	805 (30.1)	695 (30.5)	49 (32.0)	103 (33.2)	49 (32.5)
3.Organic and chemical substances, non-medical	502 (18.8)	437 (19.1)	24 (15.7)	50 (16.1)	24 (15.9)
4.Others	470 (17.6)	392 (17.2)	30 (19.6)	54 (17.4)	29 (19.2)
5.Multidrug	502 (18.8)	425 (18.6)	29 (19.0)	62 (20.0)	28 (18.5)
Clinics – n (%)					
The University Hospital Skåne, Lund	1794 (46.4)	1539 (46.7)	125 (49.4)	247 (49.8)	124 (50.0)
Odense University Hospital	501 (12.9)	419 (12.7)	28 (11.1)	50 (10.1)	28 (11.3)
Helsingborg Hospital	1372 (35.5)	1176 (35.7)	81 (32.0)	170 (34.3)	79 (31.9)
Hospital of South West Jutland	202 (5.2)	162 (4.9)	19 (7.5)	29 (5.8)	17 (6.9)

Abbreviations: CCI, Charlson Comorbidity Index; IQR, interquartile range.
*In the total cohort patients with a near-overlapping QTc interval (440-449 ms men, 440-459 ms women) are included (n =320).

In addition, prescription of QT prolonging drugs was more frequent in the group with a prolonged QTc interval. Among patients with a redeemed prescription of a single QT prolonging drug 7.5% had a prolonged QTc interval, whereas 8.8% of those taken two or more QT prolonging drugs had a prolonged QTc interval. Among the included patients, 6.5% (95% CI, 5.9-7.4) had QTc prolongation, while the prevalence of severe QTc prolongation (≥500 ms) was 0.7% (95% CI, 0.5-1.0). The prevalence of QTc prolongation in relation to specific groups of poisoning varied within the range 4.8-6.2%, with the highest prevalence in the group categorized as “others” (6.2%; 95% CI, 4.8-8.7) (Table 2).

Table 2: QTc prolongation in relation to poisoning groups

	Analgesics and drugs of abuse	Psychotropic drugs including drugs affecting the central nervous system	Chemical and biological substances, non-medical	Others	Multidrug
ICD-10 codes or definition	T39-T40, F110, F120, F140, F150, F160	T42-T44, F130, F190	T51-T65, F100, F170, F180	T36-T38, T41, T45-T50	≥2 of the described poisoning groups
N	397	805	502	470	502
QTc prolongation – n (%, CI 95%) ≥450 ms (men) ≥460 ms (women)	21 (5.3%; 3.3-8.0)	49 (6.1%; 4.5-8.0)	24 (4.8%; 3.1-7.0)	29 (6.2%; 4.2-8.7)	28 (5.6%; 3.7-8.0)

Abbreviation: CI, confidence interval.

Prognosis

Overall, the 30-day risk of all-cause mortality or cardiac arrest was 0.8% (95% CI, 0.6-1.2, n=32). Among individuals with QTc prolongation (n= 253), death within 30 days after contact to the ED occurred in 7 patients, whereas one patient suffered from cardiac arrest. Among those with a normal QTc interval (n=3616), we found 24 events during the follow-up period. The absolute risk of event within 30 days was 3.2% (95% CI, 1.4-6.1) and 0.7% (95% CI, 0.5-1.0) for patients with and without QTc prolongation, respectively.

The propensity score analysis included 248 patients with a QTc of ≥450 ms (men) or ≥460 ms (women) matched with 496 patients with a QTc interval <440 ms. Acceptable balance of baseline variables was achieved (Table 1). QTc prolongation was associated with a HR of 3.6 (95% CI, 1.0-12.2) for 30-day all-cause mortality or cardiac arrest (Table 3 and Figure 2).

Table 3: Risk assessment in the study population

Propensity score matched cohort	n	Events (No.)	HR** (95% CI)
Suspected poisoning Normal QTc interval <440 ms	496	n<5	1.0 (ref)
QTc prolongation ≥450 ms, men ≥460 ms, women	248	8	3.6 (1.0-12.2)
Diagnose of poisoning* Normal QTc interval <440 ms	310	n<5	1.0 (ref)
QTc prolongation ≥450 ms, men ≥460 ms, women	151	6	10.5 (1.2-90.0)

Abbreviations: CI, confidence interval; HR, hazard ratio. If the number of events in the analysis was less than 5 (marked by n<5), the number of patients in the strata is not shown.
*Patient who arrived with suspected poisoning and had a discharge diagnose of poisoning.
**Cox regression calculated after 1:2 propensity score matching comparing patients with QTc prolongation to patients without QTc prolongation. In this population, patients with near-overlapping ranges of the QTc interval were excluded (QTc 440-449 ms, men and 440-459 ms, women).

Subgroups and sensitivity analyses

Our results from the subgroup analysis are outlined in Appendix D. When restricting to those who also received a discharge diagnose of poisoning, we found an overall 30-day risk of 0.7% (95% CI, 0.4-1.1) and QTc prolongation yielded an overall HR of 10.5 (95% CI, 1.2-90.0). When we corrected the QT interval with the Bazett formula a total of 1112 patients had QTc prolongation (28.7%), which was associated with a HR of 1.0 (95% CI, 0.2-5.5).

DISCUSSION

In this transnational cohort of patients with suspected poisoning arriving to the ED, QTc prolongation was common (6.5%). A prolonged QTc interval was associated with a three-fold increased risk of 30-day all-cause mortality or cardiac arrest and an absolute risk of 3.2%.

This study has several strengths. First, this was a multicenter cohort study with data from two Swedish and two Danish EDs which ensured a broad representability. Use of personal identification numbers in all contacts to the hospital system in Sweden and Denmark provide the possibility to follow individual patients in and out of hospital and loss of follow-up or unmeasured registration of death did not occur. [17-22] In addition, we implemented several confounders in our propensity score model, and thus managed to control for these despite a low event-rate. We included patients who were suspected for being poisoned on arrival to the ED. These patients do – in contrast to patients identified by their discharge diagnosis – represent the clinical situation at the door in the ED. At this point, the doctors have to decide whether or not to observe the patients using telemetry.

This study also has several limitations. First of all, the design was an observational design. The ECG measures were all automatic readouts, and we did not manually validate the length of the QT intervals. However, this method has been validated in a previous Danish study using the same technique, which showed a good overall agreement between manual QTc interval and the digital record of the QTc interval with a mean difference of 1.3 ms.[8] Further, we did not exclude ECGs with diagnoses complicating QTc measuring, e.g. atrial fibrillation. We did not have information regarding previous ECGs, and we do not know if some patients had a previous ECG with QTc prolongation before arrival with suspected poisoning. The dose of drug or substance was unknown, and we were ignorant of the timing of the ECG recording in relation to peak drug concentration. The poisonings were not confirmed by blood samples or by urine tests, but were extracted from predefined ICD-10 codes. In addition, administration of diuretics and possible electrolyte imbalance were unknown.

The small number of events was a limitation in its own and did not allow for meaningful subgroup analysis. As cardiac arrest was identified based on hospital registration an eventually event of unregistered cardiac arrest, where the patient survived, is not included as an event. The number of these events is believed to be small as registration of cardiac arrest is mandatory in both the Swedish and Danish health care system. With a small number of events any miscounting of events would lead to considerable change in risk estimates. If we have overlooked one event of cardiac arrest who survived in the group of patients with QTc prolongation it would increase the absolute risk from 3.2% to 3.6%, while the risk of event in the entire study population would increase from 0.8% to 0.9%.

The event-rate in our cohort (0.8%) is in accordance with previous studies of poisoned patients (0.5-1.2%).[16,34,35] In contrast, the prevalence of QTc prolongation is substantially lower (6.5%) than in a previous study of unselected ED patients (35%).[36] This is probably due to the choice of QT correcting formula. If the Bazett formula had been chosen for main analysis, the prevalence of QTc prolongation in our study population would have been 28,7%. It is of broad consensus that the more widely used Bazett formula tends to overcorrect at heart rates at 80-90 beats per minute and above resulting in a higher prevalence of QTc prolongation.[33,37] As a high percentage of acute patients have tachycardia at arrival, this probably explains most of the difference between the occurrence of QTc prolongation in our study and in the study of unselected ED patients. The Framingham formula used in our study is considered superior compared with the more widely used Bazett formula.[37]

The clinical impact of our findings is the difference in risk of all-cause mortality and cardiac arrest within 30 days in respect to QTc prolongation. We found an absolute risk of 0.7% in patients with suspected poisoning without QTc prolongation, whereas patients with a prolonged QTc interval have an absolute risk of 3.2%, which translates into a HR of 3.6 (95% CI, 1.0-12.2). In the general population, a meta-analysis reported a pooled relative risk of 1.35 (95% CI, 1.24-1.46) for long-term mortality in patients with QTc prolongation.[7] A recent study including all patients who had an ECG recorded at the hospital for any reason reported QTc prolongation to be associated with a HR of 7.3 (95% CI, 4.10-13.05) for 30-day mortality.[37] Combined, these studies support the hypothesis that patients with a prolonged QTc are at increased risk. Whether or not this is directly linked to the increased QTc interval or due to other risk factors associated with a prolonged QTc remains unknown.

As demonstrated in our cohort the prevalence of QTc prolongation is strongly associated to the correction formula. Further, the difference between the HR calculated in the main analysis using Framingham (HR 3.6; CI 95%, 1.0-12.2) versus the sensitivity analysis using Bazett (HR 1.0; 95% CI, 0.2-5.5) is remarkable. We suspect that using the Bazett formula dilutes the association by including more patients at low risk as a result of overcorrection.

Despite the use of a propensity score model adjusting for several covariates, we cannot exclude residual confounding. From a clinical point of view, this means that the patients with a prolonged QTc probably need special care and attention. However, the needed care is not necessarily limited to telemetry and increased cardiac awareness. Of note, a ventricular arrhythmia with fatal outcome caused by drug-induced QTc prolongation, would be expected to happen within a relatively short time-interval after exposure. This was not the case in our study with the first event occurring three days after contact (see Figure 2). In addition, a QTc interval threshold for identification of patients in need of cardiac telemetry is not well-established. Unfortunately, our cohort was too small to do further subdivisions of the QTc interval.

Ventricular arrhythmias, especially torsades de pointes, are feared consequences of QT prolongation and may be the cause of death in some poisonings.[38,39] However, as torsades de pointes is a rare condition,[38,39] it is unlikely to have influenced our results.

In this cohort of patients with suspected poisoning 69.2% received a discharge diagnose of poisoning. This is in contrast to results from a previous Danish study, which found an agreement of 79% for suspected poisoning on arrival and a discharge diagnose of poisoning.[17] In our cohort, only those who had an ECG recorded were included, and several common poisonings, e.g. alcohol intoxication, are usually not followed by ECG recording.

QTc prolongation was most frequent in the group of poisoning labeled "others" (Table 2). In this group, the ICD-10 code T50.9 for unspecific poisonings was given to the majority of the patients. These patients might have been too sick to tell about their poisoning or perhaps denied to do so. This reflects a common clinical problem in the ED, and indicates that a specific poisoning diagnosis can be difficult to establish. Further, lack of precision in coding procedure may contribute to unspecific diagnoses.

In conclusion, we found QTc prolongation in a mixed population of patients with suspected poisoning in the emergency department of two Swedish and two Danish hospitals to be associated with a three-fold risk of 30-day all-cause mortality or cardiac arrest and an absolute risk of 3.2%.

Founding

This study was funded by an independent grant from The Research Foundation of Odense University Hospital. The funding sources had no role in the design of the study, data analysis or interpretation of the results.

Competing interests

ATL was supported by an unrestricted grant to the University of Southern Denmark from TrygFoundation. All other authors declare no conflicts of interest.

Author contributions

CSH designed the study, interpreted the results and drafted the paper. AP analyzed the data. CSH, AP, ATL, HKJ, UE, MB, and JLF conceived the study. ATL, AP and HKJ provided statistical advice and advice on the study design. AP, ATL, HKJ, UE, MB, and JLF critically reviewed the paper, assisted with interpretation of the results, and have approved the final edition. CSH takes responsibility for the final paper.

Data sharing statement

Due to Danish law regarding personal data we are not allowed to share data in public dataset. However, we welcome every researcher who wants to repeat the analysis or do new analysis in the dataset. Please contact professor Annmarie Lassen (Annmarie.Lassen@rsyd.dk) and she will help the researcher to get access to the data.

REFERENCES

1. Carter-Storch R, Olsen UF, Mogensen CB. Admissions to emergency department may be classified into specific complaint categories. *Dan Med J.* 2014;61(3):A4802.
2. Safwenberg U, Terént A, Lind L. Differences in Long-term Mortality for Different Emergency Department Presenting Complaints. *Acad Emerg Med.* 2008;15(1):9-16.
3. Woosley RL, Romero KA. QTdrugs List. AZCERT, Inc. https://www.crediblemeds.org/new-drug-list/. Updated August 10, 2016. Accessed December 17, 2015.
4. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 1999;20(4):278-284.
5. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol.* 2006;47(2):362-367.
6. Robbins J, Nelson JC, Rautaharju PM, et al. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. *Am J Med.* 2003;115(9):689-694.
7. Zhang Y, Post WS, Blasco-Colmenares E, et al. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology.* 2011;22(5):660-670.
8. Nielsen JB, Graff C, Rasmussen PV, et al. Risk prediction of cardiovascular death based on the QTc interval: evaluating age and gender differences in a large primary care population. *Eur Heart J.* 2014;35(20):1335-1344.
9. Panoulas VF, Toms TE, Douglas KM, et al. Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: an association driven by high inflammatory burden. *Rheumatology (Oxford).* 2014;53(1):131-137.
10. Straus SM, Sturkenboom MC, Bleumink GS, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J.* 2005;26(19):2007-2012.
11. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med.* 2009;360(3):225-235.
12. Ray WA, Meredith S, Thapa PB, et al. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther.* 2004;75(3):234-241.
13. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366(20):1881-1890.
14. Drew BJ, Califf RM, Funk M, et al. Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. *Circulation.* 2004;110(17):2721-2746.
15. Manini AF, Nelson LS, Skolnick AH, et al. Electrocardiographic predictors of adverse cardiovascular events in suspected poisoning. *J Med Toxicol.* 2010;6(2):106-115.
16. Manini AF, Hoffman RS, Stimmel B, et al. Clinical risk factors for in-hospital adverse cardiovascular events after acute drug overdose. *Acad Emerg Med.* 2015;22(5):499-507.
17. Norgaard B, Mogensen CB, Teglbjaerg LS, et al. Diagnostic packages can be assigned accurately in emergency departments. A multi-centre cohort study. *Dan Med J.* 2016;63(6):A5240.
18. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015;7:449-490.
19. Pottegard A, Schmidt SA, Wallach-Kildemoes H, et al. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol.* 2016.
20. Astrand B, Hovstadius B, Antonov K, et al. The Swedish National Pharmacy Register. *Stud Health Technol Inform.* 2007;129(Pt 1):345-349.
21. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* 2014;29(8):541-549.

22. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;24(11):659-667.
23. *Marquette^{TM} 12SL^{TM} ECG Analysis Program. Physician's Guide. 2056246-002 Revision B.* Milwaukee, WI: GE Healthcare; 13 July 2015.
24. *Läkarhandbok för Phillips DXL-algoritm för EKG. Publikationsnummer 453564149891.* Andover, MA: Phillips Medical Systems; 1 June 2009.
25. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol.* 1992;70(7):797-801.
26. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation.* 2009;119(10):e241-250.
27. Sturmer T, Joshi M, Glynn RJ, et al. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. *J Clin Epidemiol.* 2006;59(5):437-447.
28. Rassen JA, Shelat AA, Myers J, et al. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl 2:69-80.
29. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
30. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-1139.
31. Poluzzi E, Raschi E, Diemberger I, et al. Drug-Induced Arrhythmia: Bridging the Gap Between Pathophysiological Knowledge and Clinical Practice. *Drug Safe.* 2017;40:461-464.
32. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat.* 2011;10(2):150-161.
33. C. BH. An analysis of time-relations of electrocardiograms. *Heart.* 1920;7:353-370.
34. Manini AF, Nelson LS, Stimmel B, et al. Incidence of adverse cardiovascular events in adults following drug overdose. *Acad Emerg Med.* 2012;19(7):843-849.
35. Gunnell D, Ho D, Murray V. Medical management of deliberate drug overdose: a neglected area for suicide prevention? *Emerg Med J.* 2004;21(1):35-38.
36. Seftchick MW, Adler PH, Hsieh M, et al. The prevalence and factors associated with QTc prolongation among emergency department patients. *Ann Emerg Med.* 2009;54(6):763-768.
37. Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? *Journal of the American Heart Association.* 2016;5(6):e003264.
38. Al-Abri SA, Woodburn C, Olson KR, et al. Ventricular dysrhythmias associated with poisoning and drug overdose: a 10-year review of statewide poison control center data from California. *Am J Cardiovasc Drugs.* 2015;15(1):43-50.
39. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003;89(11):1363-1372.

Legends for figures

Figure 1: Flowchart of the study population

Figure 2: Kaplan Meier failure estimate

Abbreviations: QTclong = 0, patients without QTc prolongation; QTclong = 1, patients with QTc prolongation.

Figure 1: Flowchart of the study population

203x220mm (300 x 300 DPI)

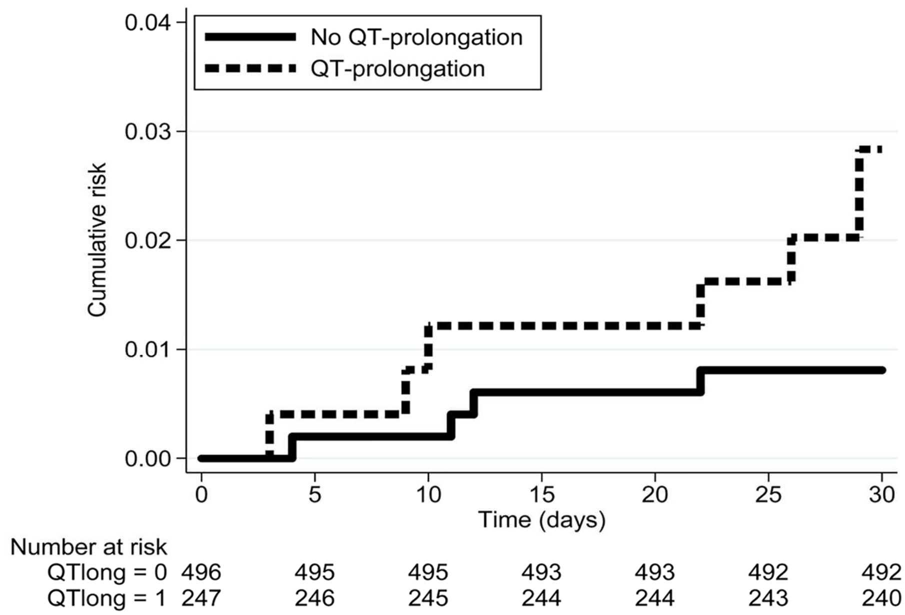

Figure 2: Kaplan Meier failure estimate
Abbreviations: QTclong = 0, patients without QTc prolongation; QTclong = 1, patients with QTc prolongation.

APPENDIX

Appendix A – Data sources

In the logistic system in the EDs of the Region of Southern Denmark and the Region of Skåne information regarding triage and presumed diagnoses are shared among the health care personal. The system also provides information on time of arrival to the ED as well as time of discharge. At arrival all patients are registered by main reason for contact. Lund and Helsingborg have 43 somatic contact possibilities, Odense and Esbjerg have 40 contact possibilities. We used these systems to identify patients with suspected poisoning.

From the electronic central ECG databases at the Region of Southern Denmark and the Region of Skåne all ECGs measures were extracted. These databases contain information of all ECGs recorded in any hospital in the respective region.

The Danish National Patient Register was established in 1977. Since 1994 diagnostic information has been recorded in accordance with ICD-10. The content includes information regarding discharge diagnoses from which comorbidities were derived. In Sweden, all health care consultations are recorded in the respective region databases. From the Skåne Healthcare Register, we retrieved information corresponding to information from the Danish National Patient Register. In these regional databases diagnoses from both the primary and secondary health care system are available. Charlson Comorbidity Index was calculated based on data extracted for a 10 year-period ending on the day of contact in the Danish data. From the Swedish database, Charlson Comorbidity Index was calculated for a 2-year period ending on the day of contact to the ED.

The Swedish National Pharmacy Register contains data on all prescriptions dispensed at pharmacies since 2005. Besides date of dispensing, name, amount, and dose of the redeemed medication are accessible from this register. The Danish National Prescription Registry provides similar information of individual-level prescription of medication since 1995. Information of redeemed prescription of QT prolonging drugs (see Appendix c.5) within 90 days before contact was obtained through these registers.

The Danish Civil Registration System contains data regarding birth, emigration, and vital status for the entire populations. Information regarding vital status in Sweden was retrieved from the Swedish population registry. The Danish Civil Registration System was established in 1968, and by law all Danish residents have a unique civil registration number of ten digits. Since 1967, all Swedish residences are assigned a ten-digit personal identity number. These unique numbers allow complete and accurate linkage between registries on an individual level.

Appendix B – Supplementary methods

ECG measurements

All ECGs were recorded and stored either in MUSE® Cardiology Information System (GE Healthcare), or by Philips Diagnostic ECG (Philips). All ECGs in our analysis were 12 lead ECGs. ECGs recorded in MUSE were later processed using the Marquette 12SL algorithm, which calculate the QTc interval using the Bazett Formula, the Fridericia Formula, and the Framingham Formula. In MUSE, the QT interval is measured as a median value from the 12 leads. ECG recorded by Philips were analyzed by the DXL-algorithm. In this algorithm, the QT interval is measured as a median value from reliable leads. A lead is defined as reliable if little variation in beat-to-beat variation. Philips provided QTc intervals corrected by the Bazett Formula and the Fridericia Formula. To correct for heart rate, we chose the Framingham Formula ($QTc_{Framingham}$ =QT + 0.154 (1-RR)). Because Philips DXL-algorithm does not routinely correct the QT interval using the Framingham Formula, we calculated the $QTc_{Framingham}$ ourselves. As we did not include RR intervals in our analysis, the formula was used in another edition than the original formula. Therefore, we used following formula for correction in ECGs recorded by Philips: $QTc_{Framingham}$ = QT + 154 (1-60/heart rate). The QRS duration was measured as a median value in both algorithms.

The Marquette 12SL algorithm defines onsets as the earliest deflection in any lead, and offsets as the latest deflection in any lead. The QT interval is measured from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead. Similarly, the QRS duration was measured from the earliest onset in any lead to the latest deflection in any lead. The Philips DXL-algorithm first identifies waveform component and measures every beat in each lead individually. After the approximate waveform locations are known, onsets and offsets are defined. Once the onsets and offsets are known, duration of intervals are calculated.

In both Denmark and Sweden ECG recording is performed by well-educated heath care personals instructed only to accept ECGs of satisfying quality. Otherwise it is considered a routine to record another ECG. If multiple ECGs were recorded in a single individual, the first ECG recorded within 4 hours after arrival was included in the analysis.

Appendix C – Codes and definitions

C.1

Codes for cardiac arrest and codes used in identifying patients with cardiac arrest	
ICD-10 codes	DI46: Cardiac arrest DI46.0: Cardiac arrest with successful recitation DI46.1: Sudden cardiac death DI46.9: Cardiac arrest unspecified
SKS codes*	**Administrative codes** AVAA07: Sudden cardiac arrest AVAA06: Sudden cardiac arrest **Procedure codes** ZZ0401: Standby for cardiac arrest **Treatment codes** BFFA6: Chest compressions BFFA60: External chest compressions BFFA60A: External chest compressions by use of mechanical chest compressions
KVÅ-codes**	DF012: Chest compressions DF017: Mechanical chest compressions DF028: Cardiopulmonary resuscitation

*SKS = Sundhedsvæsenets klassifikations system, available on http://medinfo.dk/sks/brows.php, Danish codes.
**KVÅ= Klassifikation av vårdåtgärder, available on http://www.socialstyrelsen.se/klassificeringochkoder/atgardskoderkva, Swedish codes.

C.2

Poisoning divided into groups by use of ICD-10 codes	
Analgesics and drugs of abuse	T39*-T40*, F110*, F120*, F140*, F150*, F160*
Psychotropic drugs and drugs affecting the central nervous system	T42*-T44*, F130*, F190*
Organic and chemical substances, non-medical substances	T51*-T65*, F100*, F170*, F180*
Others	T36*-T38*, T41*, T45*-T50*
Multidrug	≥2 of the above mentioned poisoning groups

C.3

Charlson Comorbidity Index*		
Condition	**Assigned weight**	**ICD-10 codes**
Peripheral vascular disease	1	I70.x, I71x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	1	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	1	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Rheumatic disease	1	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	1	K25.x-K28.x
Mild liver disease	1	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	1	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Hemiplegia or paraplegia	2	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
Renal disease	2	I12.0, I13.1, N03.2-N03.7, N05.2- N05.7, N18.x, N19.x, N25.0, Z49.0- Z49.2, Z94.0, Z99.2
Diabetes with chronic complications	2	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2- E13.5, E13.7, E14.2-E14.5, E14.7
Cancer	2	C00.x-C26.x, C30.x-C34.x, C37.x- C41.x, C43.x, C45.x-C58.x, C60.x- C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Metastatic cancer	3	C77.x-C80.x
Moderate or severe liver disease	3	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
AIDS/HIV**	6	B20.x-B22.x, B24.x

*Diagnostic codes for myocardial infarction and heart failure are not included in the index, but are included in this study as covariates.

** AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus

C.4

Variables from Charlson Comorbidity Index, included separately in the analysis	
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0

C.5

List of drugs associated with QT prolongation and risk of TdP*	
Drug category	**ATC-codes****
Alimentary tract and metabolism	Domperidone (A03FA03), Granisetron (A04AA02), Metoclopramide (A03FA01), Ondansetron (A04AA01), Pantoprazole (A02BC02)
Cardiovascular system	Amiodarone (C01BD01), Dronedarone (C01BD07), Flecainide (C01BC04), Furosemide (C03CA01, C03EB01), Hydrochlorothiazide (C03EA01, C09DA01, C09DA06, C09DA04, C09BA02), Indapamide (C03BA11), Isradipine (C08CA03), Ivabradine (C01EB17), Sotalol (C07AA07)
Genito urinary system and sex hormones	Alfuzosin (G04CA01), Mifepristone (G03XB01), Mirabegron (G04BD12), Solifenacin (G04BD08, G04CA53), Tolterodine (G04BD07), Vardenafil (G04BE09)

Systemic hormonal preparations, excl. sex hormones and insulins	Oxytocin (H01BB02), Pasireotide (H01CB05)
Anti-infectives for systemic use	Atazanavir (J05AR15), Azithromycin (J01FA10), Bedaquiline (J04AK05), Ciprofloxacin (J01MA02), Clarithromycin (J01FA09), Erythromycin (J01FA01), Fluconazole (J02AC01), Foscarnet (J05AD), Itraconazole (J02AC02), Ketoconazole (J02AB02), Metronidazole (J01XD01), Moxifloxacin (J01MA14), Posaconazole (J02AC04), Rilpivirine (J05AG05), Ritonavir (J05AE03), Roxithromycin (J01FA06), Saquinavir (J05AE01), Voriconazole (J02AC03)
Antineoplastic and immunomodulatory agents	Anagrelide (L01XX35), Bortezomib (L01XX32), Bosutinib (L01XE14), Ceritinib (L01XE28), Crizotinib (L01XE16), Dabrafenib (L01XE23), Dasatinib (L01XE06), Degarelix (L02BX02), Eribulin mesylate (L01XX41), Fingolimod (L04AA27), Lapatinib (L01XE07), Leuprolide (L02AE02), Nilotinib (L01XE08), Oxaliplatin (L01XA03), Panobinostat (L01XX42), Pazopanib (L01XE11), Sorafenib (L01XE05), Sunitinib (L01XE04), Tacrolimus (L04AD02), Tamoxifen (L02BA01), Vandetanib (L01XE12), Vemurafenib (L01XE15)
Musculo-skeletal system	Tizanidine (M03BX02)
Nervous system	Amantadine (N04BB01), Amisulpride (N05AL05), Amitriptyline (N06AA09), Apomorphine (N04BC07), Aripiprazole (N05AX12), Asenapine (N05AH05), Atomoxetine (N06BA09), Citalopram (N06AB04), Clomipramine (N06AA04), Clozapine (N05AH02), Dexmedetomidin (N05CM18), Doxepin (N06AA12), Droperidol (N05AD08), Escitalopram (N06AB10), Fluoxetine (N06AB03), Galantamine (N06DA04), Haloperidol (N05AD01), Hydroxyzine (N05BB01), Imipramine (N06AA02), Levomepromazine (N05AA02), Lithium (N05AN01), Methadone (N07BC02), Mirtazapine (N06AX11), Nortriptyline (N06AA10), Olanzapine (N05AH03), Paliperidone (N05AX13), Paroxetine (N06AB05), Pimozide (N05AG02), Pipamperone (N05AD05), Propofol (N01AX10), Quetiapine (N05H04), Risperidone (N05AX08), Sertindole (N05AE03), Sertraline (N06AB06), Sevoflurane (N01AB08), Sulpiride (N05AL01), Tetrabenazine (N07XX06), Venlafaxine (N06AX16), Ziprasidone (N05AE04)
Antiparasitic products, insecticides and repellents	Chloroquine (P01BC02), Hydroxychloroquine (P01BA02), Metronidazole (P01AB01), Pentamidine (P01CX01), Quinine sulfate (P01BC01)
Respiratory system	Diphenhydramine (R06AA02), Promethazine (R06AD02)
Various	Perflutren lipid microspheres (V08DA01)

*From QTDrug list, https://crediblemeds.org/, version December 17, 2015. Only drugs available in Denmark are included at our list. The list includes drugs with known risk of TdP, possible risk of TdP, and conditional risk of TdP.
**ATC = Anatomical Therapeutic Chemical

Appendix D – Supplementary results

Results from stratified analysis. Although further strata than shown in this table were preplanned (e.g. stratification on all poisoning groups and age), we only stratified when possible due to a small number of events.

	QTc prolongation QTc ≥450 ms, men QTc ≥460 ms, women	Normal QTc interval <440 ms, men and women	HR* (95% CI)
	Events (n)**	Events (n)**	
Suspected poisoning			
Total	8 (248)	n<5 (496)	3.6 (1.0-12.2)
Male	n<5	n<5	2.7 (0.5-16.3)
Female	n<5	n<5	4.4 (0.8-24.3)
Age ≥50 years	6 (131)	n<5	2.7 (0.7-9.9)
Odense or Esbjerg	n<5	n<5	5.8 (0.6-57.4)
Lund	n<5	n<5	1.7 (0.2-12.2)
Helsingborg	n<5	n<5	4.4 (0.4-49.2)
Confirmed poisoning			
Total	6 (151)	n<5	10.5 (1.2-90.0)
Psychotropic drugs	n<5	n<5	2.0 (0.1-32.5)

Abbreviations: HR; hazard ratio, CI; confidence interval.
*Hazard ratio from Cox regression.
**If the number of events in the analysis was less than 5 (marked by n<5), the number of patients in the strata is not shown.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1 and 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 3**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 3-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4 and 5** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **Page 5** (As we did a propensity score analysis the number of exposed and unexposed are outlined in the results because it cannot be provided before the analysis) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4, 5, and Appendix B and C**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4 and Appendix A, B, and C**
Bias	9	Describe any efforts to address potential sources of bias **Page 6**
Study size	10	Explain how the study size was arrived at **Page 4 and figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,

		describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5 and 6**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5 and 6**
		(*c*) Explain how missing data were addressed **No missing data.**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **No loss to follow-up.** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 6**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 6**
		(b) Give reasons for non-participation at each stage **Page 6**
		(c) Consider use of a flow diagram **Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 6 and 7, including table 1**
		(b) Indicate number of participants with missing data for each variable of interest **None missing**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 8**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 8 and table 3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7 and 8 including table 3**
		(*b*) Report category boundaries when continuous variables were categorized **Page 5**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Page 8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses The prevalence of QTc prolongation in relation to specific subgroups: **page 7 and table 2.** **Appendix D** includes a stratified analysis. Sensitivity analysis: **page 8 and 9.**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 9 and 10.**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 10 and 11.**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 9 and 10.**

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 12**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.