PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between QTc prolongation and mortality in patients with suspected poisoning in the emergency department – a transnational propensity score matched cohort study
AUTHORS	Schade Hansen, Camilla; Pottegard, Anton; Ekelund, U; Kildegaard Jensen, Helene; Lundager Forberg, Jakob; Brabrand, Mikkel; Lassen, Annmarie

VERSION 1 – REVIEW

REVIEWER	Kim Dalhoff Dept. Clinical Pharmacology, Bispebjerg and Frederiksberg University Hospital, 2400 Copenhagen, Denmark
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	This is a well-planned, well-executed and well-written register-based cohort study aiming at describing the prevalence of QTc-prolongation among patients admitted to emergency departments (EDs) with suspected poisonings. Further the authors planned to calculate the risk of mortality and cardiac arrest associated with QTc-prolongation. The cohort consisted of data from 2 Danish and 2 Swedish hospitals. In almost 4,000 patients the prevalence of a prolonged QTc interval was 6.5%, and there was a 3-fold increased risk of all-cause mortality or cardiac arrest 30 days after the hospital admission. Some points for consideration: 1. The included hospitals cover almost the same number of people. However, some of the hospitals may have cardiology departments in which poisoned patients are admitted to directly bypassing the ED due to e.g. the severity of the poisoning (cardiac collapse). In addition patients may be transferred immediately to the ICU due to respiratory failure. Could this affect the results of the study? 2. The authors have divided the patients into 5 different groups including a group (#1) with analgesics and drugs of abuse. However, according to appendix C4 in which the most common drugs associated with QTc-prolongation and risk of TdP are listed, analgesics occupy only a small number of the total sum. Why did the authors not concentrate on the drugs in which the potential for developing QTc-prolongation was highest? 3. Intake of two or more drugs that individually has a potential for QTc-prolongation increases the overall risk of causing a malignant arrhythmia. Is it possible to break down the group with multidrug exposure? It seems that this group in particular may have the highest risk? 4. Confounders were included in the propensity score model e.g. comorbidity measured by the use of the Charlson Index. Due to the small number of events, it was not possible to perform a subgroup analysis. It is, anyhow, interesting to know why and how this score is

	or was supposed to be implemented. It is based on 30-year-old data in which specific diseases and conditions were graded according to severity. However, the prognoses of some of these diseases or conditions have been improved over the many years from 1987, which may have changed the graduation of the severity.

REVIEWER	IGOR DIEMBERGER, MD, PHD Institute of Cardiology University of Bologna, Italy
REVIEW RETURNED	

GENERAL COMMENTS	I have found the paper interesting and informative. I would suggest to consider few other confounding factors that should be included in the limitation section if not feasible: - Presence of atrial fibrillation - Co-administration of diuretics - Electrolite unbalance - Presence of cancer. For this point I do suggest to read this paper (Diemberger et al, Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs. Eur J Clin Pharmacol. 2015 Aug;71(8):1001-9.) Finally I would analyze the presence/absence of QTc prolonging drugs not in general but according to crediblemeds classification (Poluzzi et al Drug Saf. 2017 Jun;40(6):461-464). Best regards

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. The included hospitals cover almost the same number of people. However, some of the hospitals may have cardiology departments in which poisoned patients are admitted to directly bypassing the ED due to e.g. the severity of the poisoning (cardiac collapse). In addition patients may be transferred immediately to the ICU due to respiratory failure. Could this affect the results of the study?

All patients in the cohort arrived through the emergency department, which is the same for all four hospitals. If some of the patients were transferred to another department, these patients are still included in the study. We have added the following sentence in the method section: All patients were followed for 30 days, including those transferred to other departments.

2. The authors have divided the patients into 5 different groups including a group (#1) with analgesics and drugs of abuse. However, according to appendix C4 in which the most common drugs associated with QTc-prolongation and risk of TdP are listed, analgesics occupy only a small number of the total sum. Why did the authors not concentrate on the drugs in which the potential for developing QTc-prolongation was highest?

We agree that most analgesics only occupy a small number of QTc prolonging drugs. However, we aimed to create a study reflecting the clinical situation in the emergency department. On arrival at the emergency department it might not clear what specific drug or drugs a patient with suspected poisoning has ingested. Therefore, we chose to include all patients with suspected poisonings in the cohort.

3. Intake of two or more drugs that individually has a potential for QTc-prolongation increases the overall risk of causing a malignant arrhythmia. Is it possible to break down the group with multidrug exposure? It seems that this group in particular may have the highest risk?

A relevant point to consider. We have added the following in the result section: 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.

Initially, we intended to do further subdivision regarding the group with multidrug exposure. However, it was not possible to do meaningful subanalysis due to the small number of events.

4. Confounders were included in the propensity score model e.g. comorbidity measured by the use of the Charlson Index. Due to the small number of events, it was not possible to perform a subgroup analysis. It is, anyhow, interesting to know why and how this score is or was supposed to be implemented. It is based on 30-year-old data in which specific diseases and conditions were graded according to severity. However, the prognoses of some of these diseases or conditions have been improved over the many years from 1987, which may have changed the graduation of the severity.

We agree at this point. In the estimation of the propensity score, a range of different confounders were included. We both implemented measueres related to the index admission (e.g. heart rate) and historical data – e.g. Charlson Comorbidity Index. Therefore, Charlson Comorbidity Index only accounts for a small part of the propensity score. Further, we modelled myocardial infarction and congestive heart failure as a single variable (that is, outside the Charlson estimate) as we expected cardiac diseases to be important confounders.

Reviewer 2:
1. I would suggest to consider few other confounding factors that should be included in the limitation section if not feasible:
- Presence of atrial fibrillation
- Co-administration of diuretics
- Electrolite unbalance
- Presence of cancer. For this point I do suggest to read this paper (Diemberger et al, Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs. Eur J Clin Pharmacol. 2015 Aug;71(8):1001-9.)

We agree that the mentioned confounders are highly relevant to consider. Atrial fibrillation is already mentioned in the limitation section. The presence of cancer is implemented in the Charlson Comorbidity Index. The co-administration of diuretics and electrolyte unbalance have now been added to the limitations as following text: In addition, administration of diuretics and possible electrolyte imbalance were unknown.

2. Finally I would analyze the presence/absence of QTc prolonging drugs not in general but according to crediblemeds classification (Poluzzi et al Drug Saf. 2017 Jun;40(6):461-464).

All drugs known to be associated with a risk of QTc prolongation were defined according to the definitions from crediblemeds. The drugs included in our study are defined in appendix C5. The intake of QT prolonging drugs was based on redeemed prescriptions. However, there might be a difference in compliance and the dose of prescript drug may vary among patients. Therefore, we chose to focus on whether or not a patient had a redeemed prescription for QT prolonging drugs.
We have added the suggested paper as a reference in our method section.

VERSION 2 – REVIEW

REVIEWER	IGOR DIEMBERGER, MD, PHD Institute of Cardiology, University of Bologna, Italy.
REVIEW RETURNED	15-Apr-2018

GENERAL COMMENTS	The points rised have been clearly discussed