INCIDENCE OF TORSADE DE POINTES IN A TERTIARY HOSPITAL POPULATION

Eline Vandael¹, Bert Vandenberg², Joris Vandenberghe³, Hilde Pincé⁴, Rik Willems², Veerle Foulon¹

1. KU Leuven – University of Leuven, Department of Pharmaceutical and Pharmacological Sciences, 3000 Leuven, Belgium.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2. KU Leuven – University of Leuven, Department of Cardiovascular Sciences, 3000 Leuven, Belgium; University Hospitals Leuven, Cardiology, 3000 Leuven, Belgium.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

3. KU Leuven – University of Leuven, Department of Neurosciences, 3000 Leuven, Belgium; University Hospitals Leuven, Psychiatry, 3000 Leuven, Belgium.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

4. KU Leuven – University of Leuven, Leuven Institute for Healthcare Policy, 3000 Leuven, Belgium; University Hospitals Leuven, Medical Coding Department and Management Information Reporting, 3000 Leuven, Belgium.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Corresponding author:

Eline Vandael

Clinical Pharmacology and Pharmacotherapy, KU Leuven

Herestraat 49 Box 521

3000 Leuven, Belgium

+3216/32.34.64

E-mail: eline.vandael@kuleuven.be

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Keywords:

Torsade de Pointes; QTc-prolongation; sudden cardiac death; incidence; risk score

ABSTRACT

Background:

Multiple risk factors play a role in the development of QTc-prolongation and Torsade de Pointes (TdP). Cases of TdP are underreported and data on the incidence of TdP is scarce. The aim of this study was to investigate the incidence of TdP in a Belgian university hospital and describe the characteristics of TdP-cases using a risk score.

Methods:

All cases from 2011 till 2013 coded with the ICD-9 code 427.1 in the University Hospitals of Leuven were selected. The medical files were reviewed and demographical, medical, medication and electrocardiographic data were collected. We focused on TdP-cases that were probably caused by the acquired long QT-syndrome. The RISQ-PATH score was used to quantify the risk in these cases (≥ 10 points as high risk for QTc-prolongation/TdP).

Results:

Over three years, 41 TdP-cases were identified of which 19 cases were secondary to the acquired long QT-syndrome (52.6% females, mean age of 74 ± 12 years). This corresponds with an incidence of 0.16‰/year in a hospital population. Most of the patients ($N=17$) were treated with at least one QTc-prolonging drug (most frequently amiodarone, sotalol and furosemide) of whom 12 patients with ≥ 1 QTc-prolonging drug of list 1 of Crediblemeds. Fifteen patients had an electrocardiogram in a 24-hours interval before the TdP with a prolonged QTc-interval ($\geq 450/470$ ms). All the patients had a RISQ-PATH score ≥ 10 .

169
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171 **Conclusions:**
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174 Although the incidence of 0.16%/year might seem low, this means that approximately 173 possibly
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176 lethal TdP-cases can be expected in Belgian hospitals each year. All TdP-cases were associated with a
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178 high RISQ-PATH score.
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1. INTRODUCTION

QTc-prolongation on the electrocardiogram (ECG), especially a QTc-interval of 500 ms or higher, is used as a marker for the risk of Torsade de Pointes (TdP) (1). TdP is a polymorphic ventricular tachycardia with QTc-prolongation with typical symptoms of dizziness, syncope and palpitations. TdP can end spontaneously, however, in approximately one-fifth of the cases, TdP will evolve into ventricular fibrillation leading to sudden cardiac death (SCD) (1;2). In patients with the congenital long QT-syndrome (cLQTS), each 10 ms increase in QTc is believed to increase the risk of TdP by 5-7% (1). Because of the possible lethal outcome of this adverse event, the risk of QTc-prolongation has received a lot of attention in the last decades (3).

Two general types of QTc-prolongation have been identified: the cLQTS and the acquired long QT-syndrome (aLQTS). At the moment, more than 170 cardiac and noncardiac drugs and many other patient-specific risk factors (e.g. age, female gender, cardiac and other comorbidities, electrolyte disturbances) have been linked with the aLQTS (4). The term 'reduced repolarization reserve', introduced by Roden, has emphasized the importance of the combination of multiple risk factors (genetic mutations, QTc-prolonging drugs and other risk factors) in the development of QTc-prolongation and TdP (3). Furthermore, to predict the impact of different risk factors on the QTc-interval, risk scores for QTc-prolongation and TdP are proposed in the literature (5;6). Based on a systematic review and a prospective observational study in the University Hospitals in Leuven, we developed the RISQ-PATH score. In contrast to previous published risk scores, the RISQ-PATH score allocates different points to the different risk factors and can be used in a broad clinical practice. The RISQ-PATH score intends to predict QTc-prolongation (7).

Because cases of TdP are often not recognized or reported, it is difficult to give an accurate number of the incidence of TdP. Moreover, only a part of the patients will reach the hospital alive (1;8). Only a few

studies have reported numbers about TdP in a general population. Molokhia et al. performed a retrospective study in Southwest France and found an overall incidence of drug-induced TdP/SCD-cases of 0.010%/y (8). Additionally, Sarganas et al. calculated the incidence of drug-induced TdP-cases based on an active surveillance program in Berlin. They reported an incidence of 0.0025%/y in males and 0.004%/y in females (9).

As far as we know, no numbers are available about the incidence of TdP in Belgium. The aim of this study was to investigate the incidence of TdP cases in a Belgian tertiary hospital and describe the characteristics of the cases, using the RISQ-PATH score.

2. METHODS

To address the aim, a retrospective study based on the discharge diagnostic coding in the University Hospitals of Leuven was set up.

2.1 Selection of the TdP-cases

In the University Hospitals of Leuven, all the diagnoses of hospitalized patients are retrospectively coded by the medical coding department using the International Statistical Classification of Diseases and Related Health Problems version 9 (ICD-9 codes). For this review, a database of all the patients with a diagnosis coded with the ICD-9 code '427.1 paroxysmal ventricular tachycardia' in the years 2011-2012-2013 was requested from the MIR (Management Information Reporting), the department where all these data are loaded in a Data Warehouse. Duplicate cases were removed from the database.

The electronic medical files of all the patients in the database were manually reviewed to identify cases of TdP. More specifically, the discharge letters were searched for the terms 'TdP' and 'Torsade de Pointes'. Subsequently, the identified cases were investigated more in detail to select only the proven cases of TdP caused by QTc-prolonging drugs and/or other risk factors (cases highly probably secondary

to the aLQTS). Cases with a congenital cause (previously known cLQTS or other inherited rhythm disorder documented in the electronic medical file), cases with symptoms but no registration of the TdP and cases which were probably caused by acute heart ischemia (probably not related to drugs or other risk factors) were excluded.

2.2 Data collection

For the included patients, the following data were collected out of the electronic medical file:

- Demographic data: age, gender, height, weight, body mass index (BMI), smoking habits, use of alcohol, date of the TdP event, ward where the patient was admitted and main reason of hospital admission.
- Medical data (manually collected based on free text, according to the definitions used in the RISQ-PATH score): hypertension, (ischemic) cardiomyopathy, rhythm disturbances, congenital long QT-syndrome, family history of SCD, diabetes, thyroid disturbances, central nervous system disorders (stroke, tumor, trauma, infection), HIV/AIDS, kidney and liver failure.
- Lab results (on the day of the TdP-event): serum potassium, calcium, estimated glomerular filtration rate based on CKD-EPI (eGFR) and C-reactive protein (CRP) values.
- ECG-data (maximum 24 hours before or after the TdP event): heart rate, RR-interval, QRS-duration and QT-interval. All ECGs were standard 12-lead resting ECGs (25 mm/s paper speed, 10mm/mV amplitude and 250Hz sampling rate). The ECGs were recorded using a MAC5500 of GE Healthcare with automated analysis by the 'GE Marquette 12SLTM ECG Analysis Program' (GE Medical Systems, Menomonee Falls, WI, USA).
- Accompanying events of syncope, resuscitation and sudden death.
- Medication data (on the day of the TdP-event): QTc-prolonging drugs (indication, dosing scheme and administration route).

All the included cases, the collected data and ECGs were checked by a second author with relevant experience.

2.3 Data analysis

QTc-prolonging drugs were classified based on the QTc-drug lists of CredibleMeds (list 1 = known risk of TdP, list 2 = possible risk of TdP, list 3 = conditional risk of TdP) (4). The QT-intervals were corrected with the Fridericia (if QRS < 120ms) and Rautaharju (if QRS ≥ 120ms) corrections (QTcF/R). Additionally, QTc-values corrected with the Bazett formula are reported (QTcB) (10). A moderately prolonged QTc-interval was defined as QTcF/R ≥ 450-500 ms (men) or QTcF/R ≥ 470-500ms (women); a severely prolonged QTcF/R-interval as QTc ≥ 500ms (11).

The RISQ-PATH score (Appendix 1) was used to summarize the risk factors for QTc-prolongation per patient. In the RISQ-PATH study, a cut-off of 10 points was set as high risk for QTc-prolongation (7).

Data analysis was performed using Microsoft Excel and SPSS 23 for Windows. Data are presented as mean ± standard deviation or median + range.

2.4 Ethical approval

The study protocol was approved by the ethics committee of the University Hospitals Leuven (s55548, ML9431, 17/07/2015).

3. RESULTS

3.1 Number of cases

The flow diagram of inclusions is presented in Figure 1. In total, over the three years, 1191 unique patients had a diagnosis coded as 'paroxysmal ventricular tachycardia' (1.00% of the total number of patients admitted to the hospital in 2011-2013). After reviewing each case manually, 41 TdP-cases were

the TdP (reported causes of death: 'rhythm disturbances' and 'brain death after reanimation', RISQ-PATH scores: 22.75 and 23 points); the other two were probably unrelated (palliative care and cancer).

All the patients (N=19) had a RISQ-PATH score ≥ 10 . The distribution of this risk score is displayed in Figure 2. The TdP-case with the highest RISQ-PATH score (28.5 points) was a female of 82 years old. She was admitted to the hospital with complaints of dyspnea. At the cardiology ward, an episode of TdP was registered (QTcF/R=532.0 ms). She recovered spontaneously; reanimation was not needed. The main cause of the TdP was probably hypokalemia ($K^+=3.38$ mmol/L). She was not treated with QTc-prolonging drugs. She did have several other risk factors for QTc-prolongation (hypertension, heart failure, atrial fibrillation, history of coronary disease, diabetes). The TdP-case with the second highest RISQ-PATH score (27.75 points) was a female of 84 years old. She was admitted to the emergency department with TdP (QTcF/R=488.9 ms) and in this case, a reanimation was necessary. Afterwards, she was transferred to the intensive care unit. She was treated with sotalol (list 1 of CredibleMeds) and furosemide (list 3 of CredibleMeds). Electrolytes were within the normal ranges; she did have an elevated C-reactive protein level (>5 mg/L) and an estimated glomerular filtration rate of 11 ml/min. Other risk factors for QTc-prolongation were: obesitas, diabetes, hypertension, valvular heart disease, atrial fibrillation and history of stroke.

4. DISCUSSION

In this retrospective study, a thorough analysis of TdP-cases in a Belgian university hospital was performed. Over 3 years, 19 TdP-cases probably secondary to the aLQTS were found (0.159‰/y). All patients had a RISQ-PATH score higher than 10 points.

4.1 Incidence of TdP in a university hospital and extrapolation to all Belgian hospitals

In this study, in comparison with the numbers reported in previous studies, a relatively high incidence of TdP was found (2;8;9). Per year, 6 to 7 TdP-cases were detected which were most probably caused by the aLQTS. This number remained stable over the three years (2011-2013) and can be translated in an incidence of 0.159‰/y in a hospital population. If all cases of TdP are taken into account (including caused by the cLQTS, acute ischemia or cases without proof on an ECG), the incidence increases to 0.343‰/y. These numbers must probably still be considered as an underestimation because not all TdP-cases will be recognized or registered in the electronic patient file (1).

This higher number than reported in previous studies can be explained by several factors. Firstly, in this study, the incidence was calculated for the hospital population and not translated to the general population. Consequently, a smaller denominator was used. Moreover, hospital patients can be considered to be at higher risk than the general population, because these patients are less stable and risk factors for QTc-prolongation are more common (e.g. electrolyte disturbances, use of QTc-prolonging antibiotics) (12). Secondly, in the studies of Sarganas et al. (9) and Molokhia et al. (8), the inclusion criteria of TdP-cases were stricter hence only drug-induced cases were included. In the study of Sarganas et al., the criteria of the WHO assessment tool were used to assess the possible drug etiology. Further, by using a prospective study design, they were not able to include all patients (9;13). In the study of Molokhia et al., on the other hand, patients with comorbidities or electrolyte disturbances were excluded (8).

If the incidence is recalculated for all hospital admissions in Belgium (based on the IMS Health Report: 1,643,518 hospital admissions in Belgium in 2011 (14); in the University Hospitals: 56,867 admissions in 2011 and 6 TdP-cases (0.106‰/y)), approximately 173 TdP-cases per year can be expected in Belgian general hospitals. This corresponds with approximately one TdP-case every two days and is only 4.5

times lower than the number of deaths in traffic accidents per year in Belgium (N=770 in 2011 (15)), illustrating the importance of this topic on a societal level. However, this extrapolation should be interpreted cautiously, as it is based on reported cases in a tertiary hospital where the risk of TdP might be higher than in community hospitals. Nevertheless, as mentioned above, we also believe that the number of reported cases is lower than the number of actual cases, which may compensate for a potential overestimation.

4.2 Validation of the preliminary RISQ-PATH score

All of the included TdP-cases could be linked with multiple risk factors. In 17 cases, one or more QTc-prolonging drug(s) of the QT-drug lists of CredibleMeds could be identified. The presence of multiple risk factors was already reported in previous reviews of TdP-cases by Aström-Lilja et al. (16) and Johnston et al. (17). This is also in line with the concept of 'reduced repolarization reserve' of Roden (3).

We used the preliminary RISQ-PATH score to quantify these risk factors and all the patients had a risk score ≥ 10 which was set as a high risk. We demonstrate that also in this population the RISQ-PATH score can be considered as a useful tool to predict the risk of patients, however this RISQ-PATH score still has to be validated in a large population to confirm acceptable sensitivity and specificity values. Female gender is considered as a risk factor for QTc-prolongation (3 points in the RISQ-PATH score). However, it is not yet clear if females have also more risk to develop TdP. In this study, an equal number of TdP-cases was found for males (N=9) and females (N=10).

4.3 Strengths and limitations

The strengths of this retrospective study are the structured approach and thorough analysis of the electronic patient files, leading to detailed information of the TdP-cases. Moreover, the RISQ-PATH score could be used to quantify the risk factors and to predict these cases.

Several limitations should be addressed. Genetic analyses could not be performed to investigate underlying genetic mutations. This study was limited to one university hospital and we should be cautious to extrapolate these numbers to all Belgian hospitals. As stated before, the reported incidence is still an underestimation because not all cases are recognized or reported in the electronic patient file by physicians. Furthermore, not all TdP were documented on an ECG. Finally, it is possible that some cases were missed because they were not coded with the ICD-9 code '427.1 paroxysmal ventricular tachycardia' (e.g. codes 'cardiac arrest; cardiorespiratory arrest' and 'ventricular fibrillation' (18)). However, with the coding software of 3M, used in the University Hospitals of Leuven to generate ICD-9-CM codes, the code 427.1 is automatically assigned when the keyword 'Torsade de Pointes' is entered.

4.4 Future perspectives

Further efforts are needed to obtain more accurate general incidence numbers of TdP. This study already proved that these numbers are higher than previously expected, especially in a hospital population. Secondly, the awareness and knowledge of the risk of QTc-prolongation and TdP should be improved and healthcare professionals should be encouraged to document and to report these cases in the patient files and to the concerning authorities (1;19). Finally, the use of clinical decision support systems that take into account patient-specific risk factors, by incorporating a risk score (e.g. the preliminary RISQ-PATH score), can be suggested to predict and prevent cases of QTc-prolongation and TdP in the future (20).

5. CONCLUSION

Over 3 years, 19 TdP-cases were identified which were probably secondary to the aLQTS. This corresponds with an incidence of 0.159%/y in a tertiary hospital population. Cautiously extrapolated to all hospital admissions in Belgian hospitals, approximately 173 possibly lethal TdP-cases can be expected in Belgian hospitals each year, illustrating the importance of awareness of the dangers of QTc-

prolongation of drugs and other conditions. All TdP-cases were associated with a high RISQ-PATH score.

This (preliminary) RISQ-PATH score should be tested to prevent TdP in the future.

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8. CONFLICTS OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

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10. FIGURES

Figure 1: Inclusion of TdP-cases

11. TABLES

Table 1: Characteristics of the TdP-cases

	Included patients (N=19)
Patient characteristics	Mean ($\pm$ SD, range) or number (%)
Female gender	10 (52.6%)
Age (years)	74 ($\pm$ 12, range 47-87)
Smoking	2 (10.5%)
Alcohol abuse	2 (10.5%)
Body mass index $\geq$ 30 kg/m ²	2 (10.5%)
Missing data	3 (15.8%)
Hypertension	14 (73.7%)
(Ischemic) cardiomyopathy	13 (68.4%)
(Supra)ventricular rhythm disturbances	11 (57.9%)
Familial history of sudden cardiac death	1 (5.3%)
Diabetes mellitus	9 (47.4%)
Thyroid disturbances	0
Neurological disorders	2 (10.5%)
Liver failure	1 (5.3%)
Hypokalemia ($\leq$ 3.5 mmol/L)	10 (52.6%)
Hypocalcemia ($<$ 2.15 mmol/L)	7 (36.8%)
Missing data	7 (36.8%)
Estimated glomular filtration rate $\leq$ 30 ml/min	4 (21.1%)
C-reactive protein $>$ 5 mg/L	16 (84.2%)

Table 2: QTc-prolonging drugs linked with the TdP-cases

	Number of patients (%)
≥ 1 QTc-prolonging drug of list 1 of CredibleMeds	12 (63.2%)
1 drug of list 1	3
2 drugs of list 1	3
1 drug of list 1 + 1 drug of list 2	1
1 drug of list 1 + 1 drug of list 3	3
1 drug of list 1 + 2 drugs of list 3	1
2 drugs of list 1 + 2 drugs of list 3	1
Amiodarone	6
Sotalol	4
Levofloxacin	2
Clarithromycin	1
Fluconazole	1
Haloperidol	1
≥ 1 QTc-prolonging drug of list 2 of CredibleMeds	1 (5.3%)
Venlafaxine	1
≥ 1 QTc-prolonging drug of list 3 of CredibleMeds	10 (52.6%)
1 drug of list 3	5
Furosemide	4
Pantoprazole	3
Sertraline	2
Quetiapine	1
Hydrochlorothiazide	1

12. SUPPLEMENTARY MATERIAL

Appendix 1: Components of the RISQ-PATH score (7)

RISQ-PATH score	
Risk factors	Points
Age ≥ 65 years	3
Female gender	3
Smoking	3
BMI ≥ 30 kg/m ²	1
(Ischemic) cardiomyopathy	3
Hypertension	3
Arrhythmia	3
Prolonged QTc ($\geq 450(\text{♂})/470(\text{♀})$ ms) on a baseline ECG	6
Thyroid disturbances	3
Liver failure	1
Neurological disorders	0.5
Diabetes	0.5
Potassium ≤ 3.5 mmol/L	6
Calcium < 2.15 mmol/L	3
CRP > 5 mg/L	1
Estimated glomular filtration rate ≤ 30 ml/min	0.5
For each list 1 QT-drug CredibleMeds	3 per drug
For each list 2 QT-drug CredibleMeds	0.5 per drug
For each list 3 QT-drug CredibleMeds	0.25 per drug
TOTAL	Maximum 40.5 points + sum QT-drugs

BMI = body mass index; CRP = C-reactive protein; QT-drug = QTc-prolonging drug