Drug-Induced QT Prolongation: Associations Between Risk Classifications in a Swedish Clinical Decision Support System and Clinical Outcomes

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Potential adverse drug events can be signaled in Clinical Decision Support Systems (CDSSs). This study validated a Swedish CDSS (Janusmed Risk Profile) by investigating associations between calculated risk classifications of drugs with QT-prolonging potential and registered related clinical outcomes. Subjects living in Kalmar County, Sweden, between 2011 and 2020 exposed to risk drugs (risk level I: somewhat increased risk, II: moderate increased risk, III: significant increased risk) were extracted from regional electronic health records and matched to controls (risk level 0: no known increased risk) by age, sex, and index date. Ventricular arrhythmia (VA), Torsade de Pointes, cardiac arrest and death were outcomes followed for one year. Logistic regression analysis was performed adjusted for age, sex, number of drugs, days in hospital and previous diagnosis. Among the 188,453 subjects, a higher proportion of those classified by the CDSS as having a risk of QT prolongation experienced VA compared to controls (risk level I = 0.26%, II = 0.34%, III = 0.71% vs risk level 0 = 0.17%). When adjusting for other risk factors, the association decreased, but risk level III remained significant with OR 2.1 (95% CI 1.6–2.9) compared to controls. Similar results were seen for the other outcomes. Although there was an association between CDSS risk classifications and clinical outcomes, only a few subjects are affected, and other factors, such as previous diagnosis, play an important role. The need for multifactorial CDSS algorithms is thus crucial to better guide prescribers in finding high-risk patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Clinical Decision Support Systems (CDSSs) can signal potential adverse drug events based on the drugs prescribed to a patient, but these signals might be overlooked among prescribers if considered clinically irrelevant or being featured excessively.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Are risk levels regarding QT-prolonging potential calculated in a Swedish CDSS (Janusmed Risk Profile) associated with registered related clinical outcomes in a population in a Swedish County?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Associations were found, even though the strength of these decreased significantly when adjusting for other risk factors, where having had the measured clinical outcome registered as a previous diagnosis was the predominant one. Only few subjects had related clinical outcomes, especially Torsade de Pointes, registered in the electronic health records during the one-year follow-up from the date when subjects first reached the highest calculated risk level.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study emphasizes the need for the development of multifactorial algorithms in CDSSs to more accurately predict patients with the highest risk.

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QT prolongation is a proarrhythmic effect inherent in certain drugs, potentially causing lethal side effects, including Torsade de Pointes (TdP) and other forms of ventricular tachycardia.[1] Drugs prone to cause QT prolongation and/or TdP are pharmacologically diverse and are used in a wide variety of medical conditions. Besides antiarrhythmic drugs, some antibiotics, certain psychotropics and analgesics are examples of drugs known to increase the duration of ventricular repolarization and thus cause QT prolongation and/or TdP.[2] A recent Swedish registry study showed that antidepressants and antiarrhythmics were the most prescribed risk drugs among patients with TdP.[3]

These cardiac risks have been a challenge in drug development[4] and in clinical health care.[5] In drug development, strategies for early prediction[6] and regulatory guidance[7] have been developed. To minimize the risk for patients, measures have been taken to characterize high-risk individuals[8–12] as well as the development of clinical decision support systems (CDSSs).[13–15] The ambition is to better manage these patients and possibly avoid the increased risk of sudden cardiac death associated with drug treatment.[16]

The most well-known clinical guidance system is the American classification of drugs, which is available at CredibleMeds.org.[17] There, drugs are labeled as having known risk to cause QT prolongation and/or TdP (included in List 1), having possible risk thereof (included in List 2), or having conditional risk, that is, drugs that can cause TdP under certain conditions or which create conditions that foster TdP (included in List 3).

A Swedish classification regarding potential risk of QT prolongation and/or TdP has been developed focusing on risk size/tendency contrary to CredibleMeds, which instead assesses the strength of evidence. The Swedish classification is available in the CDSS Janusmed Risk Profile[18–20] and categorizes each drug according to the extent of QT prolongation and/or TdP risk, and then summarizes the individual's potential risk according to all her prescriptions. Each patient is assigned a total risk level from this calculation.

Janusmed's knowledge databases, like many CDSSs in the field, are the so-called expert systems where risk classifications are solely determined by the individual patient's prescribed drugs and based on rules and algorithms developed by experts.[21,22] A well-known weakness of this type of system is the high number of alerts that lack clinical relevance, leading to alert fatigue, which in turn increases alert override and the risk of missing important signals.[23] Therefore, there is a need for more precise CDSSs in this domain.[24]

A recent cross-sectional study performed in the same Swedish region as this study has demonstrated that approximately 12% of all patients were prescribed or administered drugs potentially causing QT prolongation during a 120-day period in 2020.[25] This stresses the need to assess the clinical relevance of these commonly occurring alerts. One way of validating the risk signals from a CDSS could be through population-based studies utilizing data on risk drug exposure, patient variables, and clinical outcomes registered in Electronic Health Records (EHR).

This study aimed to investigate associations between calculated risk classifications of drugs with QT-prolonging potential from the Swedish CDSS (Janusmed Risk Profile) and registered related clinical outcomes.

METHODS

This study was designed as a retrospective cohort study using EHR data from Kalmar County over a 10-year period. Exposure was defined as use of drugs that together or on their own increase the potential risk of QT prolongation according to decision-support algorithms from the Janusmed Risk Profile knowledge database. The primary outcome was recorded adverse events related to QT prolongation. The study was approved by the Swedish Ethical Review Authority, Dnr 2021–03880, decision 2021-09-21, and Dnr 2024–02121-02, decision 2024-04-24.

Data sources and study population

Kalmar County is situated in the southeast part of Sweden and contains both rural and urban areas. It has one of the oldest populations in Sweden with 25% of the inhabitants being 65 years or older in 2024.[26]

The study population included inhabitants of Kalmar County, Sweden, who had at least one recorded drug dispensed or administered during the 10-year period from January 1, 2011, to December 31, 2020. Data were extracted from the regional data warehouse and included information from the EHR system Cambio Cosmic, as well as records of dispensed drugs from pharmacies. For an overview of data extraction and the selection of subjects exposed to risk drugs and controls, see **Figure 1**.

Drug data were obtained from both dispensed prescriptions at pharmacies and drugs administered in healthcare settings. Data from the EHRs of private healthcare providers were not included. However, all prescription drugs dispensed at pharmacies for the study population were included, regardless of the prescribing healthcare provider. In this study, exposure was defined as receiving drugs, or combinations of drugs, that potentially increase the risk of QT prolongation. For each day of the 10-year study period, concurrent drugs for each individual were determined based on prescription drugs dispensed at pharmacies and drugs administered in healthcare settings, as recorded in the EHR within the preceding 120 days (referred to as the exposure period). In Sweden, drugs are usually dispensed for 3 months at a time due to rules for reimbursement. Since there can be some variation and drugs are sometimes dispensed with a slightly longer time interval, one extra month was added to capture the dispensing of any chronic treatment in the "exposure period".

The rules and algorithms from the Janusmed Risk Profile knowledge database were then applied to classify each subject's risk level daily throughout the study period. Janusmed Risk Profile is a Swedish knowledge database designed to identify and signal increased risk across nine pharmacological risk categories[19,20]: Anticholinergic side effects, Risk of bleeding, Constipation, Orthostatism, QT prolongation/arrhythmia, Nephrotoxicity, Sedation, Seizures, and Serotonergic side effects. Each substance in the database has a risk score for all of the nine categories, which are summarized according to an algorithm for a patient to provide a risk level for each category.[27] In this study, only the QT prolongation risk category was used. For QT prolongation, each substance in the knowledge database has a risk score between 0 and 3. Based on the subjects' current drugs, risk scores for all drugs are aggregated using a predefined algorithm to determine an overall risk level for each subject. The risk levels are categorized according to Janusmed Risk Profile as follows: level 0 (no known increased risk, aggregated risk score of 1 or less), level I (somewhat increased risk, aggregated risk score of 2–3), level II (moderately increased risk, aggregated risk score of 4), and level III (significantly increased risk, the highest level, aggregated risk score of 5 or more, or the presence of an individual drug with a risk score of 3). For example, a patient taking amiodarone (risk score 3) would automatically be assigned the highest risk level. A patient taking citalopram (risk score 2), ciprofloxacin (risk score 2), and itraconazole (risk score 1) would reach an aggregated risk score of 5 and thus also be assigned the highest risk level. As part of this classification process, topical drugs (based on drug formulation) were excluded. In addition, only unique substances were considered in the risk assessment, that is, if a subject received the same substance multiple times within the 120-day exposure period, it was counted only once. The definition of a unique substance in Janusmed Risk Profile is based on the top

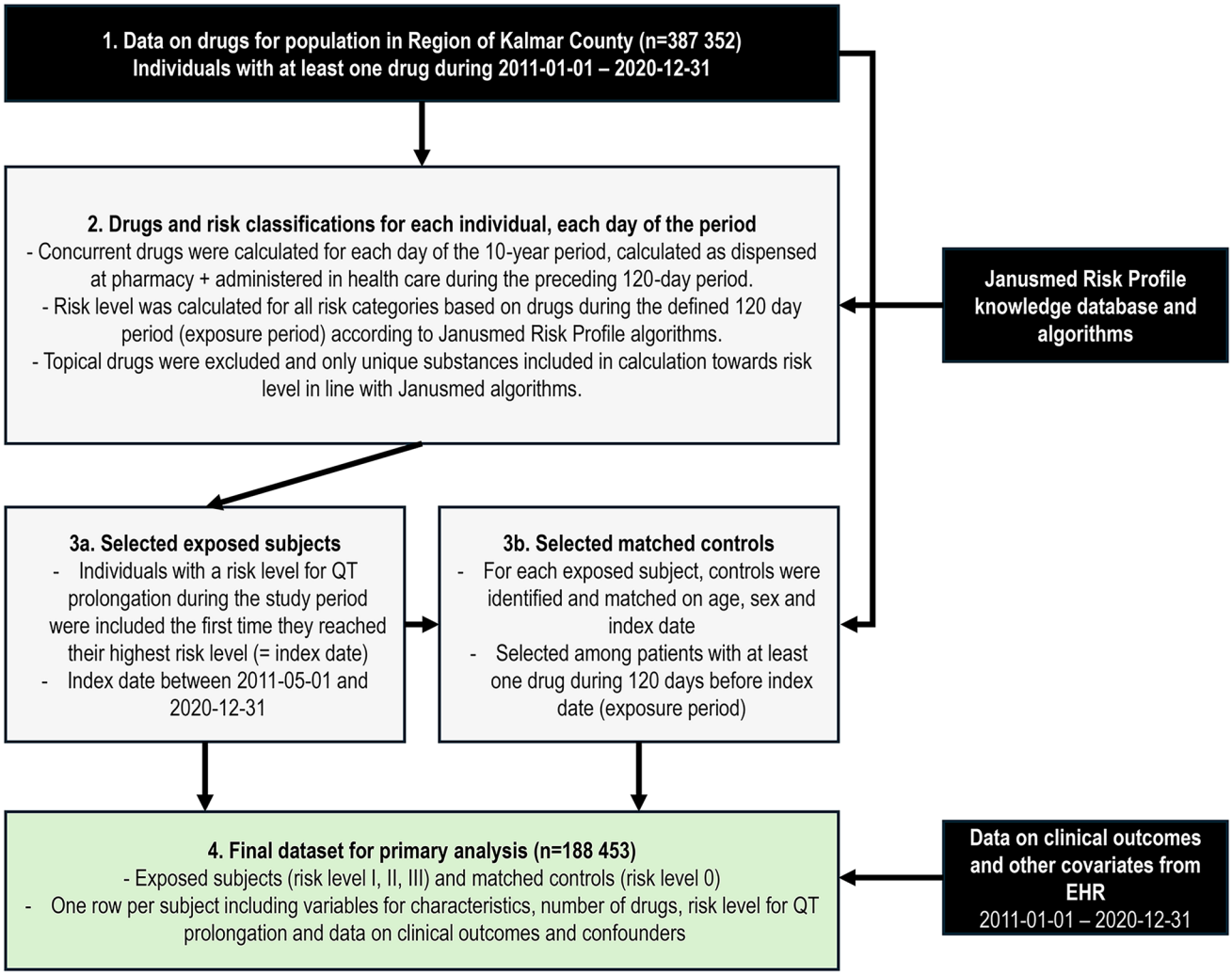

Figure 1 Overview of data extraction and selection of study population. For details about clinical outcomes see **Table 1**.

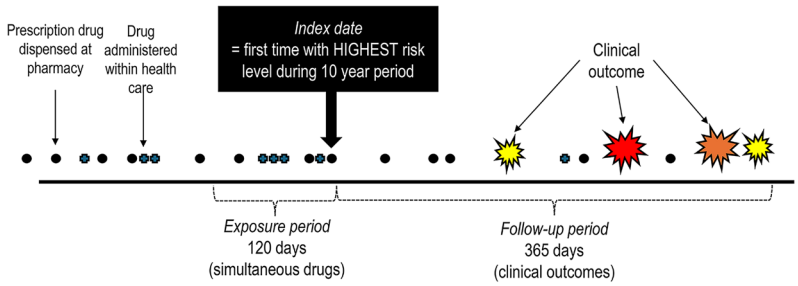

Figure 2 Explanation of index date and periods for exposure and follow-up for subjects exposed to risk drugs and controls.

parent substance ID, which is similar to the fifth level of the Anatomical Therapeutic Chemical (ATC) classification system, though some differences may exist.

Janusmed Risk Profile is not implemented in the EHR system used in Region Kalmar County but was applied retrospectively to the data for the purposes of this study. The version of the Janusmed Risk Profile rules and algorithms used was V3 from January 10, 2022. A previous publication describes the methodology of applying Janusmed Risk Profile to the retrospective data on drugs[25] (**Figure 1**).

An individual was included in the study on the first day they reached their highest risk level according to Janusmed Risk Profile, which was designated as the index date (**Figure 2**). For example, if an individual reached risk level III at any point during the study period, the index date was set as the first occurrence of this risk level. This corresponds to the day on which the drug event, in combination with other drug events from the preceding 120 days, results in the assigned risk level. Time to first outcome and the number of outcomes after the index date are assessed by identifying all outcomes occurring within 365 days after the index date, starting from the day following the index date (**Figure 2**).

Controls were individuals from Kalmar County who had at least one drug dispensed or administered within a 120-day period, with their index date set as the last day of this period. Controls were selected from

Table 1 Overview of specific diagnosis codes and events included in the four outcomes, based on data registered in the electronic health record (EHR)

Outcome	Specific outcomes (registrations included)	Diagnosis code (ICD-10)
Ventricular arrhythmia (VA)	Paroxysmal ventricular tachycardia	I47.2
	Short-duration ventricular tachycardia	I47.2A
	Long-duration ventricular tachycardia	I47.2B
	Ventricular tachycardia, torsades de pointes	I47.2C
	Paroxysmal tachycardia, unspecified	I47.9
	Ventricular fibrillation and ventricular flutter	I49.0
	Long QT syndrome	I49.8E
	Other specified cardiac arrhythmias	I49.8
	Cardiac arrhythmia, unspecified	I49.9
Torsade de Pointes (TdP)	Short-duration ventricular tachycardia	I47.2A
	Long-duration ventricular tachycardia	I47.2B
	Ventricular tachycardia, torsades de pointes	I47.2C
Cardiac arrest (CA)	Cardiac arrest	Diagnosis codes starting with I46
Death	Date for when a subject dies registered in the EHR. No data on cause of death.	–

individuals who did not reach an increased risk level during the study period (i.e., they are not study subjects) and are matched by age (in full years), sex, and index date. Controls were randomly selected from the same population and data source (the EHR system Cambio Cosmic). Controls may have drugs classified with a risk score of 1, provided their total risk level does not exceed the threshold for risk level I.

For everyone (both exposed subjects and controls), the number of unique drugs was calculated based on unique ATC codes at the 5th level. The number of drugs was determined from both dispensed prescriptions and drugs administered in hospitals during the exposure period, with the index date set as the last day of the 120-day period.

Clinical outcome and other covariates

The outcomes in this study consisted of events or other registrations in the EHR that may indicate an adverse drug event (ADE) related to QT prolongation. Although the outcome of interest is primarily TdP, other outcomes were used as well to capture potential events. A significant number of TdP events may be underreported, as they might be recorded under alternative diagnosis codes or as death, rather than explicitly coded as TdP. Therefore, four different outcome categories were used in this study: (1) ventricular arrhythmia (VA, including TdP), (2) TdP, (3) cardiac arrest (CA), and (4) death (**Table 1**).

For each outcome category, it was assessed whether an event occurs within 365 days following the index date (yes/no) starting the day after the index date, as well as the number of days until the first occurrence and the total number of outcome registrations. Additionally, for the analysis, data on prior diagnoses and days of hospitalization during the year preceding the index date were collected as additional covariates.

Analysis

The analysis included four groups based on risk classification, where risk levels I, II, and III were considered exposed subjects, while controls were those classified as risk level 0 according to Janusmed Risk Profile. Descriptive analyses were conducted to compare the four groups in terms of age, sex, number of drugs, number of days hospitalized during the year prior to the index date, proportion of individuals using specific drug groups, and proportion of individuals experiencing an outcome during the follow-up year starting the day after the index date.

For each of the outcomes Kaplan–Meier curves were created with the number of days one year after the highest Janusmed risk prediction as the independent variable stratified by the risk levels. The curves were produced using the R package Survival.[28]

For statistical analyses, variables were categorized. Based on birth dates, age was categorized into three categories: younger than 65 years, 65–79 years, and 80 years or older. The number of drugs was categorized into three categories: 1–4 drugs, 5–9 drugs, or 10 drugs or more. The number of days hospitalized was also categorized into three categories: no hospitalization during the period, 1–9 days of hospitalization or 10 days or more of hospitalization.

Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated using logistic regression. In the models, the odds ratios were calculated against the reference categories of women, subjects younger than 65 years, those taking 1–4 drugs, no hospitalization during the studied period, and Janusmed risk level 0—no known increased risk.

The statistical analysis was conducted using IBM SPSS Statistics version 29 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp). All plots were made using the R package ggplot2.[29]

Sensitivity analysis

Given that a previous diagnosis may influence the risk of getting the same diagnosis again, we fitted several different models. In addition to the adjusted model including previous diagnoses as a variable displayed in the Results section (**Figure 4**), two additional adjusted models were created: a model not considering any previous diagnosis at all, and a model in which those with a previous diagnosis were filtered out of the models (see Supplementary Material S1).

In addition, a separate analysis was made with index date as the day each subject reached their first risk level for QT prolongation, instead of using the highest risk level during the period to decide the index date. For that design, no matched controls were selected. Data was used for descriptive analysis only.

Table 2 Description of the population ($n = 188,453$) divided in the four study groups: exposed level I, II, III and level 0 (control group). Risk level is decided by Janusmed classification. Control group (risk level 0) are matched by age, sex and index date. Proportion (%) with different groups of drugs that are classified as increasing the risk of QT prolongation according to Janusmed Risk Profile, grouped according to ATC-classification

	Risk level 0	Risk level I	Risk level II	Risk level III
Number of subjects	93,981	67,368	12,828	14,276
Age (median; IQR)	53; 38	51; 38	58; 35	62; 31
Proportion female	56.6%	56.6%	56.8%	56.4%
Total number of drugs (median; IQR)	2; 3	4; 5	8; 7	11; 8
Number of days hospitalized previous year (median; IQR)	0; 0	0; 0	0; 3	1; 7
Proportion with Alimentary tract and metabolism drugs (ATC A)	24.9%	37.4%	55.9%	70.0%
Proportion with Cardiovascular drugs (ATC BC)	40.6%	40.1%	57.6%	69.3%
Proportion with Mental health disorder drugs (ATC NR)	44.0%	70.6%	91.9%	95.8%
Proportion with Antimicrobial agents (ATC JP)	18.7%	50.5%	55.1%	65.7%
Proportion with Antineoplastics (ATC L)	2.3%	3.5%	7.7%	10.7%
Proportion Genito-urinary system drugs (ATC G)	19.4%	18.4%	23.8%	27.7%
Proportion with risk drug from other ATC-groups	42.2%	40.0%	52.2%	61.9%

RESULTS

Description of study population

A total of 94,472 subjects exposed to drugs with potential QT-prolonging effects between 2011 and 2020 were extracted from the EHR in Region Kalmar County. A majority (71.3%) pertained to Janusmed risk level I while 13.6% and 15.1% of the subjects were categorized in risk level II and III, respectively. These subjects exposed to risk drugs were matched by age, sex and index date to a control group (risk level 0) consisting of 93,981 subjects. The median age varied between 51 and 62 years. Approximately 57% of the included subjects were female. When comparing subjects with different Janusmed Risk Profile levels it was found that higher age and a larger total number of prescribed drugs co-varied with higher risk level (**Table 2**).

Clinical outcomes

A small proportion (0.02–3.15%) of the included subjects had at least one of the studied clinical outcomes registered in the EHR within a year after their index date. Of 188,453 subjects in the study 477 (0.25%) had VA diagnosed. The number of subjects with registered TdP was 33 (0.02%) and subjects with a registered CA were 276 (0.15%). Over all 5,755 (3.15%) of the included subjects died within a year from the index date (**Table 3**).

When stratifying according to risk level from Janusmed, there was a coherent pattern across the different clinical outcomes, with one exception, namely TdP. In all the rest of the outcomes, a higher Janusmed risk level meant a higher risk of each outcome. The cumulative incidence of VA ranged from 0.17% in subjects with Janusmed risk level 0 to 0.71% in subjects with risk level III. The cumulative incidence of CA and death ranged from 0.07% to 0.47% and from 1.34% to 14.28%, respectively. When measuring TdP diagnoses, the cumulative incidence ranged from 0.01% to 0.07% with the marginally largest proportion in subjects with Janusmed risk level II (**Table 3**).

Male sex, higher age, longer stays in hospital and larger number of concomitant drugs were, together with a previous diagnosis, all predisposing factors for the various clinical outcomes (**Table 3**).

Temporal aspects

The influence of time on each clinical outcome according to Janusmed Risk Profile level is displayed in the Kaplan–Meier graphs in **Figure 3**. The higher crude probability of outcome in higher Janusmed risk levels is most visible in relation to survival and least visible in TdP. The differences between Janusmed risk levels can be observed relatively soon after the index date.

Results from bivariate and multivariate analysis

For each of the clinical outcome odds ratios, both crude (section A, C, E, and G) and adjusted to variables included in the model (section B, D, F, and H) are presented in **Figure 4**.

While a congruent pattern with regard to Janusmed risk level in relation to each outcome, except in TdP, was seen in the bivariate analysis, this pattern was less clear when the influence of the other included variables was adjusted for in the multivariate analysis. Janusmed risk level III remained significant compared to risk level 0 when analyzing VA (although OR was reduced from 4.1 to 2.1) and death (although OR was reduced from 10.6 to 2.5) while becoming nonsignificant in TdP and CA.

Throughout the multivariate analyses, having had a previous diagnosis (except for death obviously) was the variable strongest associated with registered clinical outcomes ranging from OR 59.7 in CA to 464.4 in TdP.

The pattern of the other included variables in the multivariate analysis showed that male sex, higher age, longer hospitalization and larger total number of drugs stayed statistically significant in VA, CA and death, while in TdP merely male sex stayed significant.

Sensitivity analysis

Besides comparing crude and adjusted odds ratios two further analyses were performed: one where the previous diagnosis variable was left out and one when only subjects without the respective previous diagnosis were included (see Supplementary Material S1). Similar results as in the multivariate analysis were observed.

A separate analysis was made with the index date as the day each subject reached their first risk level for QT prolongation, instead of using the highest risk level during the period to decide

Table 3 Clinical outcomes registered in EHR during the one-year follow-up from index date presented as cumulative incidence (N) and absolute risks (%) according to stratified variables

	Ventricular arrhythmia (VA)			Torsade de Pointes (TdP)			Cardiac arrest (CA)			Death		
	No outcome	Outcome	Absolute risk	No outcome	Outcome	Absolute risk	No outcome	Outcome	Absolute risk	Survived	Died	Absolute risk
	(N)	(N)	(%)	(N)	(N)	(%)	(N)	(N)	(%)	(N)	(N)	(%)
Sex												
Female	106,466	213	0.20%	106,670	9	0.01%	106,559	120	0.11%	103,903	2,776	2.67%
Male	81,510	264	0.32%	81,750	24	0.03%	81,618	156	0.19%	78,795	2,979	3.78%
Age												
0–64	123,965	182	0.15%	124,138	9	0.01%	124,100	47	0.04%	123,465	682	0.55%
65–79	44,567	196	0.44%	44,746	17	0.04%	44,632	131	0.29%	42,578	2,185	5.13%
80-years	19,444	99	0.51%	19,536	7	0.04%	19,445	98	0.50%	16,655	2,888	17.34%
Days hospitalized												
0 days	150,803	266	0.18%	151,056	13	0.01%	150,987	82	0.05%	149,532	1,537	1.03%
1–9 days	28,522	145	0.51%	28,653	14	0.05%	28,553	114	0.40%	26,618	2049	7.70%
10-days	8,651	66	0.76%	8,711	6	0.07%	8,637	80	0.93%	6,548	2,169	33.12%
Number of drugs												
1–4 drugs	113,258	148	0.13%	113,402	4	0.00%	113,368	38	0.03%	112,770	636	0.56%
5–9 drugs	48,423	174	0.36%	48,584	13	0.03%	48,531	66	0.14%	47,281	1,316	2.78%
10 or more	26,295	155	0.59%	26,434	16	0.06%	26,278	172	0.65%	22,647	3,803	16.79%
Previous diagnosis												
No	187,395	364	0.19%	188,399	27	0.01%	188,096	252	0.13%			
Yes	581	113	19.45%	21	6	28.57%	81	24	29.63%			
Janusmed risk level												
0	93,820	161	0.17%	93,975	6	0.01%	93,911	70	0.07%	92,736	1,245	1.34%
I	67,196	172	0.26%	67,359	9	0.01%	67,261	107	0.16%	65,554	1814	2.77%
II	12,784	44	0.34%	12,819	9	0.07%	12,796	32	0.25%	11,916	912	7.65%
III	14,176	100	0.71%	14,267	9	0.06%	14,209	67	0.47%	12,492	1784	14.28%
Total	187,976	477	0.25%	188,420	33	0.02%	188,177	276	0.15%	182,698	5,755	3.15%

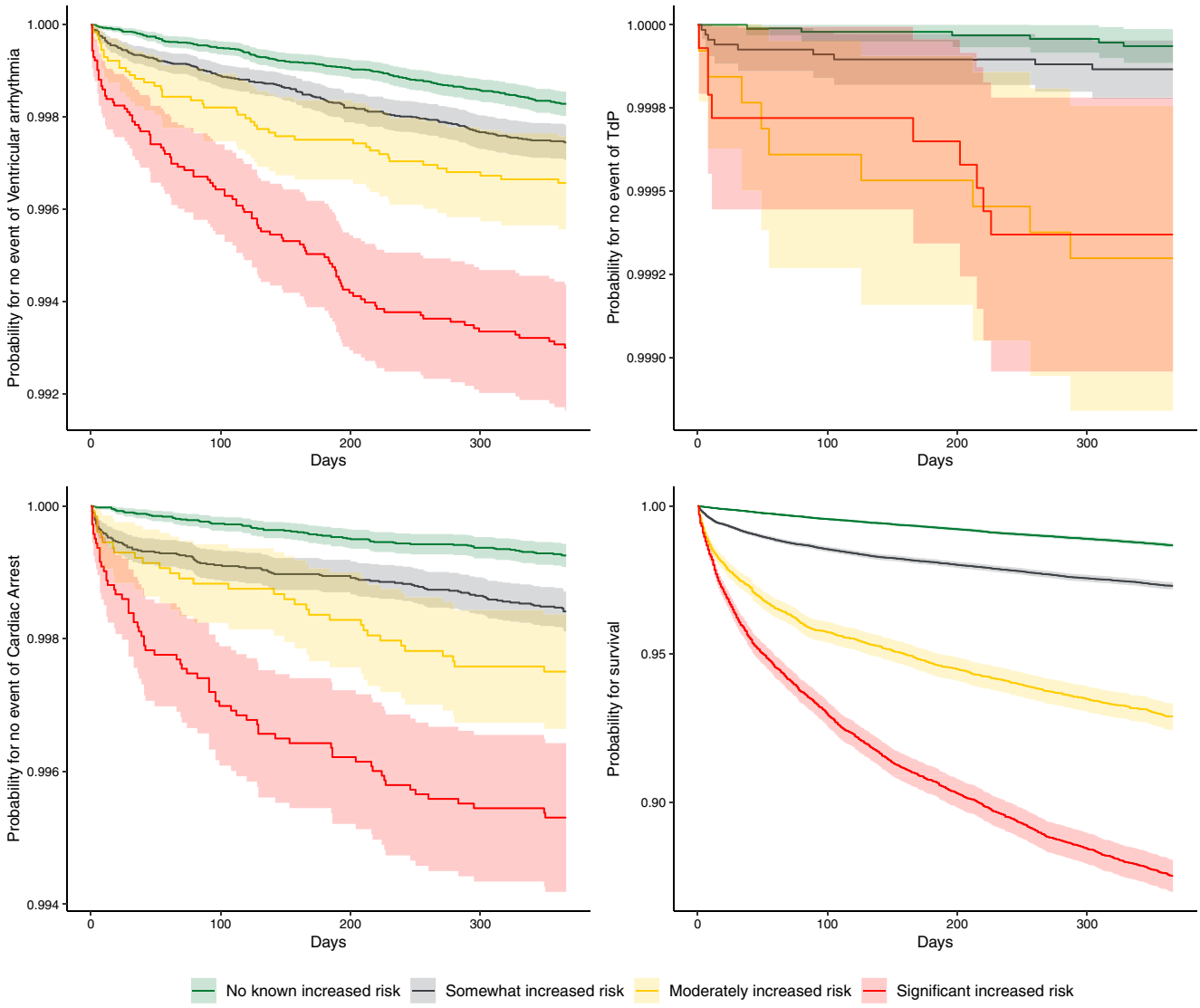

Figure 3 Temporal influence on crude outcomes. Kaplan–Meier graphs displaying effect on outcome probability in relation to Janusmed risk levels (level 0 = no known increased risk, level I = somewhat increased risk, level II = moderate increased risk, and level III = significant increased risk).

the index date. This gives the same number of exposed individuals ($n = 94{,}472$); however, 96.5% ($n = 91{,}157$) end up in risk level I, 2.8% ($n = 12{,}828$) in risk level II and only 0.7% ($n = 696$) in risk level III. When using this index date, results show that 0.32% ($n = 290$) of individuals in risk level I get the outcome VA during the follow-up year for this index date; 0.53% ($n = 2{,}619$) in risk level II get the outcome, and 1.01% ($n = 7$) of those in risk level III get the outcome.

DISCUSSION

The results in this study indicate that even among subjects classified in the highest risk category with QT-prolonging drugs, fewer than one percent experienced VA or CA, and an even smaller proportion had TdP registered in the EHR during the one-year follow-up. Even though outcomes were rare, the calculated risk levels from Janusmed were found to be associated with the occurrence of the various studied outcomes.

Furthermore, the current findings highlight that multiple additional factors significantly influence the risk of VA and other cardiac outcomes, suggesting that incorporating variables such as age, sex, and prior diagnoses into Janusmed Risk Profile assessments could be beneficial.

One downside to existing Swedish CDSSs aiming to guide prescribers is, as acknowledged, the fact that they only take the use of risk drugs into account. In concordance with the present study several other risk factors for arrhythmia and cardiac events besides the use of QT-prolonging drugs have been previously suggested. Family history of long QT syndrome, heart disease, electrolyte disturbance comprise some of these other risk factors.[8,11,30] Moreover, earlier studies have suggested that risk signals related to drug prescriptions need to be seen in a medical comprehensive context to better guide prescribing physicians.[20,31]

Several strategies exist to enhance the specificity of CDSSs and reduce alert fatigue, including expert-driven grading systems and

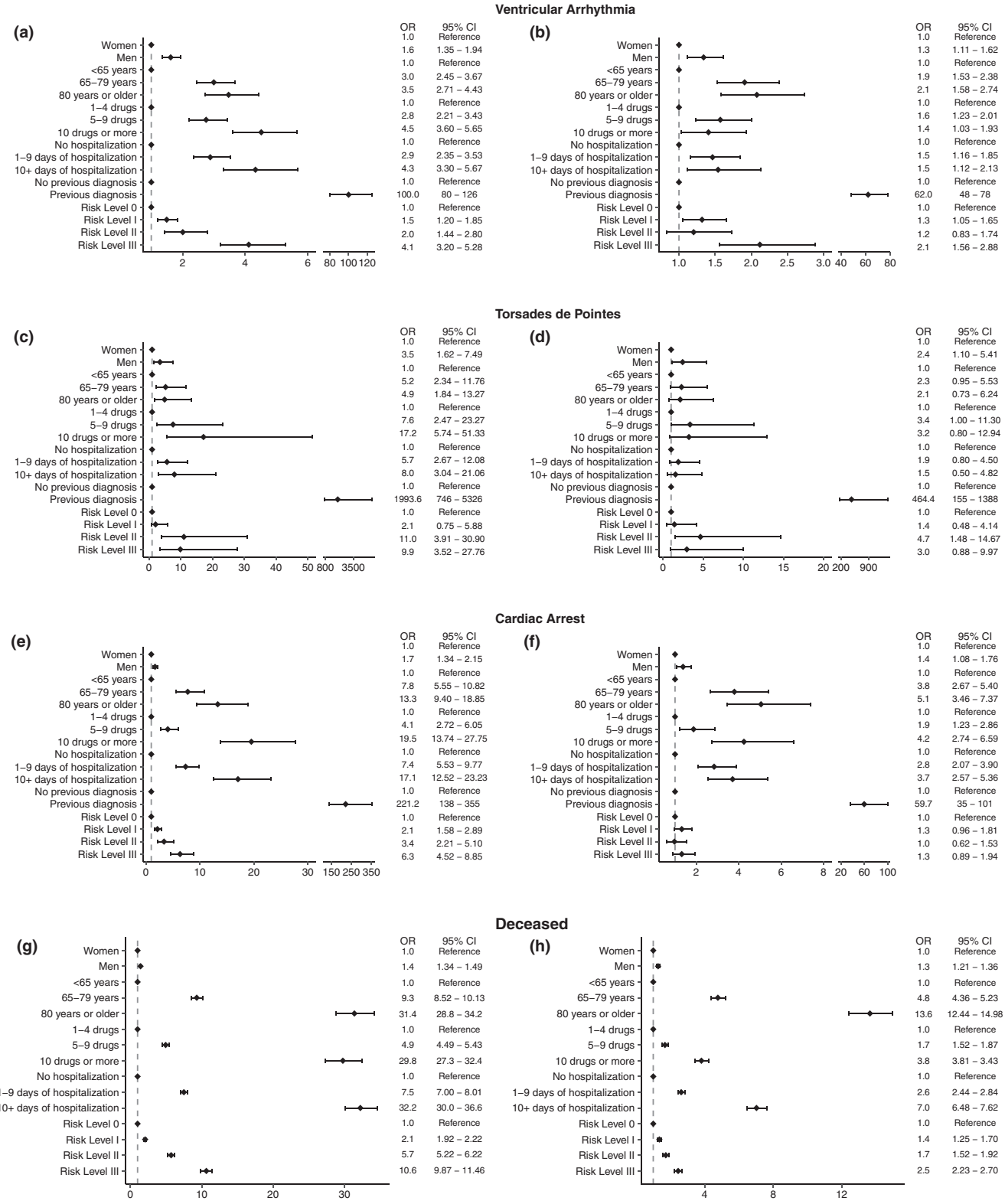

Figure 4 Bivariate and multivariate analysis. In the left sections (**a**, **c**, **e**, and **g**), crude odds ratios for each variable in relation to respective outcome is presented. In the right sections (**b**, **d**, **f**, and **h**), corresponding adjusted odds ratios are displayed ($n = 188\,453$).

machine learning-based methods.[22,32] Multifactorial risk scores to predict QT prolongation among hospitalized patients have been developed[13,33] and assessed.[34,35] A reduction in the prescribing of QT-prolonging drugs and a reduced risk of QT prolongation among the hospitalized patients was found related to the implementation of the multifactorial CDSS.[34] When assessing clinical

responses to a CDSS in another study, they varied according to the type of QT-prolonging risk drug although ordering ECG was the most common action taken overall.[36] Alert fatigue in the area of QT-prolonging drug CDSSs has been suggested previously in a study where 51% of the signals were indeed overridden.[37]

The researchers behind the current study are continuing their work on machine learning models to improve the prediction of ADEs. Swedish guiding principles for the use of this type of real-world data in CDSSs development have been published.[21]

In relation to previous studies, the results from this study are congruent when exploring some of the other risk factors, for example, advancing age and the use of QT-prolonging drugs.[8,38] While females are generally considered at higher risk for QT prolongation and TdP,[39,40] the current study instead found male sex to be an independent risk factor for all the related outcomes. This could possibly be explained by the higher risk in men to suffer from a general cardiac event such as VA[41] or sudden cardiac death.[42] Due to the low number of TdP cases in the current study, no significant conclusions regarding sex differences related to TdP incidence can be drawn.

A review of the evidence of various risk factors for QT prolongation[43] found strong evidence supporting the use of diuretics, antiarrhythmic drugs and the drugs from CredibleMeds list 1 while the use of digoxin, statins and drugs from CredibleMeds list 2 or 3 together with a history of a prolonged QTc-interval/TdP was considered as having little or no evidence. As that study posed as a validation of CredibleMeds, where risk classification is based on level of evidence, our current study could be considered a validation of Janusmed Risk Profile regarding QT-prolonging drugs, where instead risk classification is based on occurrence/rates.

This study has several strengths, including its population-based design and a long study period of 10 years, covering both primary and hospital care. The inclusion of data on both dispensed prescriptions and administered drugs within health care provides a comprehensive view of drug use. In addition, risk classifications are based on a high-quality knowledge database developed by experts. However, some limitations should be noted. It is uncertain whether drugs classified as concurrent are actually being used simultaneously, and the control group differs from exposed individuals in terms of the number of drugs among other things. Generally, data from EHRs are known to lack some information and some of the registered information is of low quality. The fact that TdP and other drug-induced long-QT syndromes are very likely underdiagnosed and the number of unreported cases is probably great[44] is likely true in this study as well. In addition, there are some things that might bias the results. There are differences between exposed subjects and matched controls at index date, which might introduce bias. The multivariable logistic regression analysis handles some of these differences but not all. The way index date was selected and controls matched may introduce a risk that exposed individuals were, to a greater extent than controls, included at a later stage in their disease trajectory, which may have led to a higher burden of comorbidities during follow-up. Additionally, the fact that controls were unexposed throughout the entire period may introduce bias. Some clinical outcomes are nonspecific, and it cannot be determined whether they are drug-related with this design. The presence of missing data, such as drugs or outcomes, may have introduced bias if the missingness was not completely at random. Lastly, as the study is limited to one region, generalizability to other populations is uncertain.

Future studies should examine associations between calculated risk classifications regarding drugs with QT-prolonging potential and registered clinical outcomes with other designs and in other populations. The present study focuses on one of the risk categories of the nine categories in Janusmed Risk Profile. There are ongoing studies for some of the other categories in the research group behind the present study. Furthermore, it should be explored how CDSSs can be improved to reduce alert fatigue in general, and specifically for QT prolongation. There is some evidence that CDSSs in general,[45] and Janusmed specifically,[46] can lead to positive effects. However, since the ability of CDSSs to predict ADEs does not necessarily lead to an actual improvement in outcomes, future studies should examine if the introduction of CDSSs could in fact reduce ADEs such as the clinical events in the present study.

CONCLUSIONS

Although there is an association between Janusmed risk classifications and clinical outcomes only a few subjects are affected, and other factors, such as previous diagnosis, play an important role. The need for multifactorial CDSS algorithms is thus crucial to better guide prescribers in finding patients at the highest risk of outcomes related to QT-prolonging drugs.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

ETHICS STATEMENT

Approved by the Swedish Ethical Review Authority, Dnr 2021–03880, decision 2021-09-21, and Dnr 2024–02121-02, decision 2024-04-24.

CONSENT

Consent of participants was not required for this study using retrospective data. The study did not affect the health care of included subjects. Social security numbers (Swedish personal number) were not exposed during the work; instead a pseudonymized code representing each unique subject was used.

AUTHOR CONTRIBUTION

O.N. and T.H. wrote the manuscript; T.H., O.N., O.B., A.L., M.L.A., B.W., and P.B. designed the research; T.H., O.N. and O.B. performed the research; T.H, O.B., and P.B. analyzed the data.

DATA AVAILABILITY STATEMENT

Data are not made available due to legal and ethical restrictions. Data were obtained from a third party. For questions, please contact the corresponding author. For questions about code or details about analysis, please contact the corresponding author.

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