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ORIGINAL RESEARCH ARTICLE

Investigating the Additive Interaction of QT-Prolonging Drugs in Older People Using Claims Data

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Abstract

Introduction Drugs that potentially prolong the QT interval carry the risk of life-threatening Torsades de pointes (TdP) ventricular arrhythmia.

Objective The objective of this study was to investigate the potential additive risk for ventricular arrhythmia with concomitant prescriptions of QT-prolonging drugs.

Methods Claims data for persons aged ≥65 years between 2010 and 2012 in Germany were analyzed and all cases hospitalized for ventricular arrhythmia were selected. In a case-crossover analysis, exposure with QT-prolonging drugs according to the Arizona Center for Education and Research on Therapeutics (AZCERT) classification of 'known,' 'conditional,' and 'possible' TdP risk was determined in respective event and control windows preceding hospitalization. Conditional logistic regression was applied to derive odds ratios (ORs).

Results Among 6,849,622 health-insured persons, we identified 2572 patients newly hospitalized for ventricular arrhythmia. Drugs with 'known' risk were more frequently prescribed in the event window than in the control window (309 vs. 239; $P < 0.001$). The number of drugs with an attributed 'known' risk of TdP was significantly associated with hospitalization for ventricular arrhythmia (OR: 2.22; 95% confidence interval [1.51–3.25]; $P < 0.001$), while increased risk estimates were also obtained upon categorization into one and two or more drugs compared with no drugs for the combined group of drug with 'known' (1.52 [1.16–2.00]) and 'conditional' risk (2.20 [1.42–3.41]). Pairwise comparisons and trend tests based on these classification categories could not demonstrate a significantly increased risk of two or more drugs compared with one drug.

Conclusion Beyond suitable single-drug classifications for QT-associated risk estimation, the situation when there is co-prescription of several drugs appears to be complex and may not be extrapolated to all possible multi-drug combinations.

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Key Points

The risk of hospitalization because of ventricular arrhythmia was shown to be higher when drugs with an attributed propensity to prolong QT and induce Torsades de pointes were involved (Arizona Center for Education and Research on Therapeutics [AZCERT] classification).

While distinct comparisons between one and two or more drugs trended towards increased risks in multi-drug combinations, the elevated risks did not appear to be supra-additive or synergistic, thus questioning warnings that put more emphasis on the second prescription than on the first, which can by itself carry serious risk for a patient with a higher baseline risk.

Considering the rather complex modulations of ion channels involved in the interplay of depolarizing and repolarizing currents, the extrapolated additivity of single QT-prolonging drugs remains to the elucidated, most reasonably based on each combination of distinct drugs.

1 Introduction

Drug–drug interactions (DDIs) are a potential cause for the adverse drug reactions (ADRs) that account for many hospital admissions in older people [1–5]. Various ADRs can be managed [6] and even prevented by thoughtful prescribing [7–9]. However, it is not always clear how co-medication modulates the risk of untoward effects, such as in situations where several drugs exerting the same unwanted effect are administered concurrently. In particular, concomitant usage of drugs prolonging the electrocardiographic QT interval is common in older people [10], but the risk related to this has not been thoroughly investigated and empirical information is scarce and often even contradictory [11–13]. While it is commonly assumed that the QT interval will increase along with the number of co-administered QT-prolonging drugs, this is not substantiated by evidence and recent results from the Rotterdam study even suggest that this is not the case [14].

The frequency-corrected QT interval (QTc) is a measure for ventricular depolarization and repolarization measured using an electrocardiogram (ECG) [15]. The prolongation of this ECG phenomenon is a marker of arrhythmogenic risk of certain drugs that may increase the propensity of serious polymorphic ventricular tachycardia (Torsades de pointes [TdP]). Among the risk factors for prolongation of cardiac repolarization, and thus life-threatening ventricular arrhythmias, are advanced age, female sex, electrolyte disturbances, genetic predisposition, structural heart disease, drugs interfering with cardiac ion channels, and combinations of these factors [16–20].

Mechanistically, several drug-induced increases in depolarizing currents and/or decreases in repolarizing currents can contribute to the complex phenomenon of drug-induced QT interval prolongation [18, 21]. A major site of DDI is the human ether-à-go-go (hERG)-related potassium channel. In vitro, different drugs can interact differently with the hERG channel and this interaction can be additive or even antagonistic and sometimes depends on the sequence of administration [22, 23]. Common sense assumptions of additive toxicities of hERG modulators may not be valid in the complexity of cardiac repolarization processes generally: in addition to the direct interaction with hERG, altered trafficking of the channel subunit and mechanisms involving sodium and calcium currents can also contribute to TdP generation [24]. While it is undisputed that individual drugs can concentration-dependently increase the risk for TdP and that co-administered inhibitors of their clearance can further increase this risk (pharmacokinetic DDI [25–27]), clear evidence for a pharmacodynamic interaction in vivo is currently lacking.

Outcome information on ventricular arrhythmia as a rare, clinically relevant complication of drug-induced QT prolongation can be validly extracted from hospital admission codes in claims data [28–30]. Claims data also supply the most comprehensive information on drug utilization with a large sample size [31]. Using these advantages, we determined single and overlapping exposure to potentially proarrhythmic drugs of patients being admitted because of ventricular arrhythmia. In a case-crossover analysis as a self-controlled design to control for fixed and also unmeasured covariates within individuals, we aimed to evaluate the influence of time-varying drug exposure and whether the anticipated additive pharmacodynamic interactions affecting cardiac repolarization really translate into ADRs and thus hospital admissions.

2 Methods

2.1 Data and Study Sample

Analyses were based on a nationwide sample of claims from health-insured persons from the ‘Statutory Health Insurance Fund’ AOK (‘Allgemeine Ortskrankenkassen’) covering approximately 30% of the German population. The population consisted of older people aged ≥65 years

within 3 years from 2010 until the end of 2012. Anonymized claims data were used including medication prescription data, documented *International Classification of Diseases, 10th edition* (ICD-10) in its German modification (ICD-10-GM) [32] coded diagnoses from outpatient and inpatient care, and inpatient information with regard to the admission date and the diagnosis leading to admission. In German claims data, outpatient diagnoses are coded by physicians on a quarterly basis; inpatient diagnoses include admission, discharge, and secondary diagnoses for the respective hospital stay. Cases were selected according to the study outcome within 2011 and 2012 as determined using the ICD-10-GM admission code for ventricular arrhythmias (I47.2), which has been validated as a claims data code showing a positive predictive value of between 80 and 90% [28, 29]. However, these estimates are partly derived from discharge diagnoses. Of note, more than one admission diagnosis is very rare in German claims data, making it impossible to use these data for sensitivity analyses. In Germany, by law, retrospective claims analyses do not require ethics committee approval.

2.2 Determination of Drug Exposures

Exposure classification was based on drugs being unequivocally identified in the medication prescription data by their ATC (Anatomical Therapeutic Chemical) code and PZN ('Pharmacy Central Number', a unique identification number for pharmaceutical products in Germany [33]). Information on ingredients, package size, dosage form, and dose were obtained from the AiD*Klinik*® drug information and decision support system based on the MMI database (MMI Pharmindex, Neu-Isenburg, Germany).

Drugs under investigation were selected as published on the CredibleMeds® website of the Arizona Center for Education and Research on Therapeutics (AZCERT) [34] and chosen by national approval status and prescription frequencies as given in the prescription report of the German healthcare system [35]. According to the AZCERT classification, we used three risk categories ('known,' 'conditional,' and 'possible' TdP risk) [34] (see Electronic Supplementary Material 1). Drug prescription durations were estimated using a previously established method that considers longitudinal drug coverage [36]: comparing the accumulated dose and the elapsed time from consecutive prescriptions for the drug under investigation gives an estimate of the actual daily dose and dividing the dispensed package size by the estimated average dose yields the duration of drug exposure. If only one prescription was registered for an active drug product, we divided the package size by a standard dose. Because older adults may receive different doses, we extracted recommended standard doses for this age group from the summary of product characteristics (see Electronic Supplementary Material 1). To account for gaps and overlaps in redemptions due to incomplete adherence [37] or lost prescriptions [38], we presumed that health-insured persons have drug stocks lasting up to 15 days due to incomplete compliance ('15-day rule' [37]), added apparent overlaps up to a maximum overlap duration corresponding to 25% of the quantity of the last overlapping prescription [38], and applied common recommendations to fill apparent gaps between prescriptions using prospective filling [39]. In the framework of the applied case-crossover design, we defined exposed patients as those with at least 1 day of exposure within the respective control window or case window (Fig. 1).

Addressing potential pharmacokinetic modulations of drug exposure, we first checked the AZCERT combinations that occurred (see Electronic Supplementary Material 2) manually for at least moderate pharmacokinetic interactions using a large drug interaction database (AiD*Klinik*® drug information system). Beyond this key step to disentangle purely pharmacokinetic mechanisms from the combinations present, we also searched for further prescription redemptions of other at least moderate pharmacokinetic inhibitors according to the US Food and Drug Administration (FDA) classification [40] in event and control windows as an additional consolidation step.

2.3 Study Design and Statistical Analysis

Patient characteristics were displayed as frequencies, proportions, or means with standard deviations and complemented by descriptive *P* values obtained from testing

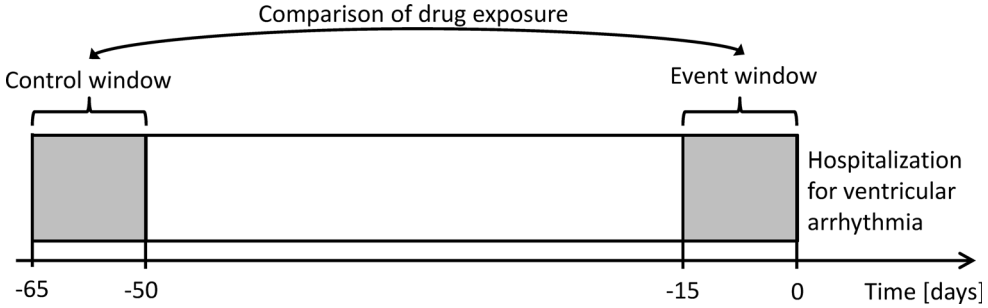

Fig. 1 Illustration of the case-crossover design with control and event windows

proportions based on the Chi-square approximation or *t* tests. Likewise, exposure with QT-prolonging drugs according to AZCERT [34] was determined as a frequency in the event and control windows prior to a hospitalization for ventricular arrhythmia.

A case-crossover design [41] using conditional logistic regression [42] was applied to investigate additive effects of drugs potentially prolonging the QT interval. Thus, the conditional logistic model was conditioned on the individual. As a self-controlled design, the method ultimately controls for between-person confounding [43], controls for immeasurable confounders in claims data (among others, congenital and familial long-QT syndromes) [30], and is efficient for rare acute events (i.e., events with a rapid onset) with transient exposures [44].

In our main analyses, we chose the event period beginning 15 days before the date of admission for ventricular arrhythmia and a 15-day control period 50 days earlier (i.e., 50–65 days before admission) (Fig. 1). The number of utilized drugs in event and control periods was calculated in total and for all three AZCERT TdP risk categories [34]. Resulting variables were included either as continuous or categorized predictors with zero (none), one, or more drugs potentially prolonging the QT interval in conditional logistic regression models [42]. This analysis aims to address the study's primary objectives, i.e., to determine associated risks related to the number of drugs and for distinct pairwise comparisons (e.g., one vs. two or more drugs).

We had a secondary interest in the specific investigation of the addition of a 'conditional' risk drug in the presence of a strong risk factor (e.g., a 'known' risk drug). Therefore, we also measured interaction beyond the multiplicative logistic regression model on an additive scale following the concept of Rothman [45]. Accordingly, the AZCERT categories of 'known' risk and 'conditional' risk were investigated, leaving out 'possible' risk drugs for which evidence is lacking regarding actually occurring events. Calculation of the relative excess risk due to interaction (RERI), the proportion of disease among those with both exposures that are attributable to their (statistical) interaction (attributable proportion [AP]), and the synergy index (S) were complemented with confidence intervals calculated by approximation [46, 47].

To compare the risks between zero, one, or more drugs, pairwise comparisons and trend tests were applied in vectors of contrast coefficients [48]: Tukey contrasts were used to test many-to-many comparisons and Marcus contrasts were used to test ordered risk trends between the distinct groups of zero, one, and more drugs. Considering these sets of orthogonal contrasts, appropriate adjustment for multiple testing is warranted.

Various sensitivity analyses were conducted in order to assess the consistency of the results obtained (see Electronic Supplementary Material 3). Lengths of event and control window periods and their distance were the subject of sensitivity analyses as recommended by Maclure and Mittleman [49]. Event and control windows had to lie within the follow-up period, which comprised the 24 months of 2011–2012; cases were selected within this period according to their date of hospitalization for ventricular arrhythmia. Before the follow-up period, we defined a run-in period in 2010 for use as a sensitivity analysis to test potential bias by 'depletion of susceptibles.' Using this timeframe for the run-in period, we excluded patients susceptible to cardiac arrhythmia, as indicated by inpatient and outpatient diagnosis codes in the corresponding co-morbidity group of the Elixhauser index [50]. In another sensitivity analysis, we excluded patients with recent acute coronary syndromes (in the follow-up period) prior to their admission for ventricular arrhythmia.

All tests were two-tailed, 95% confidence intervals were calculated, and P values <0.05 were considered statistically significant. Statistical analyses were performed using the R software/environment version 3.2.0 [51].

3 Results

In our data source including 6,849,622 health-insured persons, we identified 6899 cases (0.1%) who were hospitalized for ventricular arrhythmia in 2011–2012, of whom 4327 already had an arrhythmia diagnosis during the run-in period according to the co-morbidity grouping. Excluding these patients (though not for sensitivity analyses), 2572 cases remained in the primary analysis set. We descriptively compared this case set with a random sample of the original dataset with regards to particular patient characteristics. To give a few examples, cases included significantly more males and a higher proportion of patients with pre-existing co-morbidities such as cardiac illnesses (e.g., valvular heart disease or congestive heart failure), diabetes, or renal impairment (Table 1). Drug exposure to potentially QT-prolonging drugs was stratified into categories of 'known,' 'conditional,' and 'possible' TdP risk.

To describe drug administration numerically, more QT-prolonging drugs were prescribed in event periods, while only drugs with 'known' risk for QTc prolongation, and thus a substantially higher risk of actual TdP arrhythmia, were significantly more often prescribed (Table 2). No specifically pharmacokinetic processes could be identified as influencing actually occurring combinations (see Electronic Supplementary Material 2). In total, we counted 1018 QT-prolonging drugs in all AZCERT categories with 'known,' 'conditional,' or 'possible' risk into the event window, while 972 of these drugs fell into the control

Table 1 Characteristics of patients admitted to hospital because of ventricular arrhythmia in selected cases compared with a random sample of older adults from the total data source

	A: Total cases (ventricular arrhythmia) ($n = 6899$)	B: New cases (primary analysis set)[a] ($n = 2572$)	C: Random sample of older adults ($n = 499{,}998$)	B vs. C: *P* value[b]
Demographics				
Age (mean ±SD)	75.4 ± 6.31	75.3 ± 6.58	76.3 ± 7.60	<0.001
Sex: female (%)	29.5	34.8	60.3	<0.001
Co-morbidities[c] (%)				
Congestive heart failure	53.3	27.3	22.8	<0.001
Cardiac arrhythmia	62.7	[a]	25.7	[a]
Valvular heart disease	28.3	13.2	11.6	0.010
Pulmonary circulation disorders	8.77	3.30	3.77	0.215
Peripheral vascular disorders	30.7	22.1	17.5	<0.001
Hypertension (complicated and uncomplicated)	85.1	75.8	78.7	<0.001
Paralysis and other neurological disorders	9.47	8.24	10.3	<0.001
Chronic pulmonary disease	31.5	24.7	23.4	<0.001
Diabetes mellitus (complicated and uncomplicated)	45.3	40.2	34.8	<0.001
Hypothyroidism	12.5	8.16	11.2	<0.001
Renal failure	30.3	15.8	14.0	0.009
Liver disease	15.7	13.1	12.7	0.467
Peptic ulcer disease excluding bleeding	3.13	2.37	2.72	0.275
Lymphoma and malignant diseases	18.6	15.8	15.9	0.865
Rheumatoid arthritis	8.04	7.50	8.16	0.228
Coagulopathy	11.3	4.00	4.39	0.341
Fluid and electrolyte disorders	15.9	7.04	10.3	<0.001
Anemia	6.61	5.09	5.27	0.694
Alcohol abuse	3.26	2.95	2.60	0.262
Drug abuse	0.91	0.89	0.77	0.473
Psychoses	1.32	1.71	2.03	0.244
Depression	18.4	16.9	20.7	<0.001

SD standard deviation

[a] Primary analysis set of cases excluded patients with prior arrhythmia diagnosis

[b] *P* value either for comparing proportions based on the Chi-square approximation or comparing continuous values based on the *t* test

[c] Categories according to Elixhauser groups

window. Among the patients exposed to any AZCERT drug in the control window or the event window (or both) ($n = 1259$), we observed that 36.9% of drug combinations differed between the two observation windows.

For analytical purposes, the drugs in the three AZCERT categories and their interaction terms were included as continuous predictor variables in a conditional logistic regression model (Table 3, part A). Significant associations with hospitalization for ventricular arrhythmia were obtained only for the main effect of drugs with 'known' TdP risk, whereas statistical significance was just missed for drugs with 'conditional' risk. Drugs with 'possible' risk yielded a point estimate of a null effect and were thus not considered in the next conditional logistic regression model, which assessed the risk of admission for ventricular arrhythmia for categories of zero, one, or more drugs with 'known' and/or 'conditional' TdP risk (Table 3, part B). Categories with one or more drugs showed a significantly increased risk of hospitalization for ventricular arrhythmia compared with the absence of such drugs. A larger effect size was obtained for the category with two or more potentially QT-prolonging drugs. In general, results were notably consistent in sensitivity analyses (see Electronic Supplementary Material 3).

Pairwise comparisons confirmed the findings listed in part B of Table 3 that both categories of one or more drugs displayed significantly increased risk estimates (Fig. 2) while not providing evidence of significantly higher risks

Table 2 Potentially QT-prolonging drugs during the event period and control window

Drug use	Cases with admission due to ventricular arrhythmia ($n = 2572$)		P value[a]
	Control window	Event window	
Drugs with known risk[b]	239/210	309/255	<0.001/0.291
Amiodarone	68/32	107/60	
Azithromycin	3/3	4/2	
Ciprofloxacin	16/10	21/12	
Citalopram	79/54	84/58	
Clarithromycin	5/1	8/6	
Domperidone	6/3	9/7	
Dronedarone	2/2	4/2	
Escitalopram	2/1	3/2	
Flecainide	10/9	11/9	
Haloperidol	5/2	10/5	
Levofloxacin	9/4	10/7	
Moxifloxacin	1/0	5/4	
Sotalol	18/11	19/13	
Drugs with conditional risk[b]	1038/778	1068/812	0.228/0.212
Amitriptyline	54/35	52/30	
Doxepin	25/18	19/14	
Fluoxetine	3/2	2/2	
Furosemide	225/115	261/137	
Hydrochlorothiazide	685/184	692/200	
Paroxetine	4/2	4/2	
Sertraline	7/5	8/7	
Quetiapine	9/7	10/6	
Drugs with possible risk[b]	165/143	169/151	0.748/0.607
Alfuzosin	21/9	18/8	
Clomipramine	3/1	3/2	
Mirtazapine	62/31	64/38	
Norfloxacin	1/0	1/1	
Olanzapine	3/1	3/1	
Promethazine	15/8	13/8	
Risperidone	23/13	26/16	
Roxithromycin	2/0	6/1	
Tizanidine	3/3	3/3	
Tolterodine	5/3	4/3	
Trimipramine	9/7	12/8	
Venlafaxine	10/4	12/5	

Data are given as total use (n)/combination use (n)

[a] P value comparing proportions of exposed cases among all cases ($n = 2572$) based on the Chi-square approximation

[b] Classification according to the Arizona Center for Education and Research on Therapeutics [AZCERT] website [34]; drugs with small cell counts were omitted in this tabulation (e.g., amisulpride, erythromycin, imipramine, nortriptyline, and ondansetron). A complete list of actually occurring combinations is available in Electronic Supplementary Material 3

of prescriptions of two or more potentially proarrhythmic compounds than prescription of only one. Nevertheless, trend tests generally suggested that adding QT-prolonging drugs to the medication regimen increases the risk of hospitalization because of ventricular tachycardia.

4 Discussion

In this thorough and comprehensive analysis of additive effects of drugs potentially prolonging the QT interval, drugs with an attributed propensity to prolong the QT

Table 3 Case-crossover analysis of drugs potentially prolonging the QT interval and their risk for hospitalization because of ventricular arrhythmia

Variable	Estimate	Standard error	OR	95% CI (OR)	*P* value
A: Continuous predictors					
Drugs with 'known' TdP risk	0.80	0.20	2.22	1.51–3.25	<0.001
Drugs with 'conditional' TdP risk	0.22	0.13	1.24	0.97–1.60	0.094
Drugs with 'possible' TdP risk	−0.08	0.28	0.92	0.53–1.62	0.784
Interaction between drugs with 'known' and 'conditional' risk[a]	−0.25	0.22	0.78	0.51–1.19	0.252
Interaction between drugs with 'known' and 'possible' risk	0.35	0.47	1.41	0.56–3.56	0.461
Interaction between drugs with 'conditional' and 'possible' risk	0.09	0.30	1.09	0.61–1.96	0.774
Interaction between drugs with 'known,' 'conditional,' and 'possible' risk	−0.11	0.56	0.89	0.30–2.70	0.841
B: Categorical predictors among drugs with 'known' and 'conditional' risk of inducing TdP ($n = 2412$)					
1 drug	0.42	0.14	1.52	1.16–2.00	0.003
≥2 drugs (median = 2)	0.79	0.22	2.20	1.42–3.41	<0.001
Categorical predictors among drugs with 'known' risk of inducing TdP only ($n = 1542$)					
1 drug	0.43	0.25	1.54	0.95–2.50	0.079
≥2 drugs (median = 2)	1.91	1.11	6.77	0.76–60.0	0.086
Categorical predictors among drugs with 'conditional' risk of inducing TdP only ($n = 2160$)					
1 drug	0.35	0.17	1.42	1.01–2.00	0.041
≥2 drugs (median = 2)	0.29	0.31	1.33	0.73–2.44	0.351
Categorical predictors among drugs with 'possible' risk of inducing TdP only ($n = 1492$)					
1 drug	−0.15	0.39	0.86	0.40–1.85	0.695
≥2 drugs (median = 2)	−0.15	0.91	0.86	0.15–5.01	0.865

Two separate conditional logistic regression models were fitted in which drug numbers were used as continuous (A) or categorized (B) predictor variables

CI confidence interval, *OR* odds ratio, *TdP* Torsades de pointes

[a] Accounting for interaction as departure from additivity, additive interaction measures proposed by Rothman [45] with CIs calculated by approximation [46, 47] yielded relative excess risk due to interaction (RERI) = −1.69 (95% CI −2.87 to −0.51), attributable proportion (AP) = −2.17 [95% CI −4.48 to 0.14], and synergy index (S) = −0.151

interval and induce TdP (AZCERT category 'known') were indeed associated with an increased risk of hospitalization because of ventricular arrhythmia. In contrast, the number of drugs with an attributed propensity to prolong QT but without convincing evidence for TdP induction ('possible') and QT-prolonging drugs that induce TdP only in the presence of co-factors ('conditional') were not associated with hospital admission due to ventricular arrhythmia in our population, thus confirming the usefulness of such a classification (Table 3, part A).

It is well-established that drugs that cause pharmacokinetic DDIs that increase the exposure of TdP-inducing drugs ('known') will also further prolong the QT interval [27] and increase arrhythmia risk (e.g., domperidone [30]). Therefore, at an individual patient level, dose-related or rather exposure-related effects can have a major impact on adverse events. In our pharmacoepidemiological analysis at the population level, we carefully excluded clearly pharmacokinetic processes from specific drug combinations and, thus, focused on additive pharmacodynamic effects by isolating the risks associated with the large number of drugs with a propensity for QT prolongation.

Potential additive proarrhythmic effects were deemed possible for some drugs, in particular those with a higher propensity ('known' TdP risk) of adverse events due to QT prolongation, yet not necessarily for all drugs across the categories.

This conclusion is based on significantly more drugs with such a higher propensity being identified in event periods (Table 2), and a significant association of their use with ventricular arrhythmia in conditional logistic regression models as a continuous predictor (Table 3, part A). While a direct comparison between situations with one and situations with more than one QT-modulating drug(s) revealed no difference in the admission risk, trend tests suggested that any addition of QT-modulating drugs to the medication can increase the risk estimate (Fig. 2). The point estimates of the pairwise comparison between situations with one or more drugs and those with zero drugs were of a similar magnitude, however, which puts the

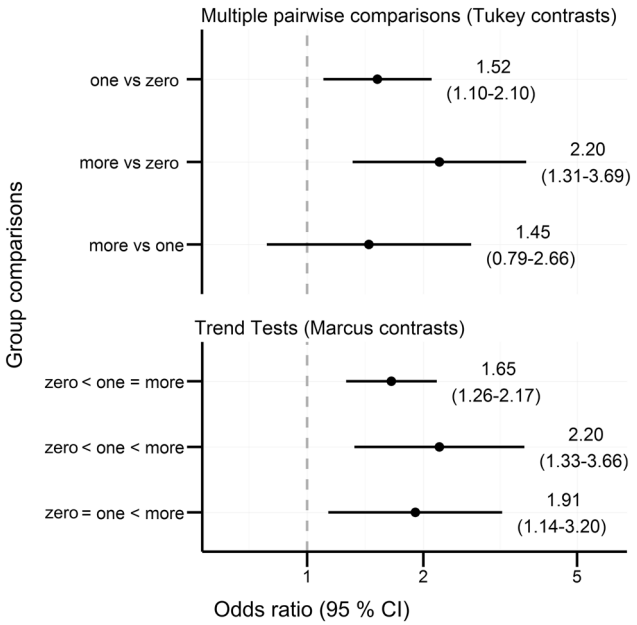

Fig. 2 Multiple comparison procedures in conditional logistic regression models of categorical variables for the number of QT-prolonging drugs with 'known' and 'conditional' Torsades de pointes risk (zero (none), one, and more). Odds ratios derived from parameter estimates of simultaneous inference are displayed with 95% family-wise confidence intervals. Pairwise comparisons of exposure groups were conducted using Tukey contrasts and trend tests were conducted using Marcus contrasts [71]. *CI* confidence interval

insignificant finding into a clinical perspective and suggests that it is not necessarily deserving of more attention than exposure with a single high-risk drug in general. Therefore, the various general warnings relating to the combination of QT-prolonging drugs and concerning contraindications noted on many drug labels appear to be inappropriate in many instances. While close QT monitoring is mandatory in all drugs with a 'known' and 'conditional' risk of TdP, these and other findings [14, 52, 53] question the concept of generally withholding drugs unless sound clinical evidence suggests to do so.

Obviously, the absence of evidence cannot rebut the thesis of an elevated risk of concomitantly prescribed drugs and comparisons between one or more drugs may have lacked statistical power to reject the Null hypothesis of no difference. The power of statistical models is often driven by the number of events and in the particular situation of the case-crossover design is also driven by the changes between the control window and the event window. It can be hypothesized that the power of the model may be limited given that the drug treatment is intended for long-term use as a low level of separation between event and control windows is expected. In contrast, the statistical power was sufficiently high to be able to detect differences between one and no drugs.

Beyond statistical power, there are mechanistic and physiological aspects to be considered. Although exposure–response relationships are likely relevant for QT prolongation, infinite prolongation of the QT interval is not possible because it will ultimately reach a plateau (saturable relationship) [17, 54]. Therefore, addition of a further QT-prolonging compound when maximum individual QT prolongation has already been reached will probably not increase the arrhythmia risk further. For example, our negative RERI estimate between drugs with 'known' and 'conditional' risks suggested a less than additive relationship based on confidence intervals of less than zero. Clinical examples corroborate this phenomenon: when terfenadine, a drug with a known TdP risk, was combined with paroxetine, a drug with a conditional TdP risk, the QT prolongation induced by terfenadine was not altered [55]. Similarly, no additional QT prolongation was observed when two drugs with a 'known' risk of TdP (ondansetron and droperidol) were combined [52]. Moreover, even if an additive QT prolongation occurs, this does not necessarily result in the frequent occurrence of ventricular arrhythmia [56]. Therefore, these findings indicate that the arrhythmia risk depends on the nature of the administered QT-prolonging drugs and co-medication, whereas the importance of the net number of such drugs as a risk modulator is still unclear and, if existent, probably minor and linked to specific AZCERT categories. Predictions of the risk of QTc-prolonging drug combinations will likely be more precise when the mechanistic co-factors that can increase or mitigate the arrhythmogenic risk of drug combinations (e.g. by modulating different ion channels) are comprehensively considered [18, 21].

The current understanding of the nature of QT prolongation suggests that functional alterations and interactions among various components controlling cardiac repolarization modulate both the QT interval and also the risk for drug-induced arrhythmia [21]. Drug treatment is only one component of several "effect amplifiers" [21] and QT interval alone will not closely reflect proarrhythmic risks (e.g., AZCERT 'possible' risk category) for a number of drugs [18]. Thus, whenever risk is to be estimated, risk factors including patient characteristics such as advanced age, female sex, bradycardia, congenital long-QT syndrome, or electrolyte disturbances (particularly hypokalemia) [16, 57, 58] need comprehensive consideration. The self-controlled case-crossover analysis that we applied inherently controls for these co-morbidities and co-factors. In this framework, the individual themself at a different timepoint serves as the best possible experimental control.

Interestingly, our aged population unexpectedly included more male cases of ventricular arrhythmia. Although sex differences in QTc duration tend to decrease with advancing age [59], TdP is still more frequent in female

older people [60]. In addition, while considerable evidence confirms the validity of the coding of ventricular arrhythmia in claims data [28–30], it is currently unknown whether admission in these patients was triggered by TdP or by other forms of ventricular arrhythmia; given the seriousness of both, any association with drugs is of interest and potential importance. As shown in this and earlier analyses [28–30], admission for ventricular arrhythmia is a rare and even more rarely drug-induced event that neither directly reflects QT prolongation nor exclusively reflects TdP or drug-induced hospitalizations. Another limitation of the data is that sudden cardiac death before reaching a hospital also cannot be identified. All of these factors may have contributed to the fact that we unexpectedly found more males in the case set of our study. However, a sensitivity analysis excluding patients with recent acute coronary syndromes yielded similar results and thus underpins the validity of the data and that the enrichment strategy to exclude patients with a previous diagnosis of cardiac arrhythmia.

When exploring the impact of multi-drug exposure, the clinical risk of combined prescription of QT-prolonging drugs depended on drug characteristics (e.g., AZCERT drug class) and was not clearly elevated when these drugs were combined. Therefore, based on the available evidence, a pharmacodynamic interaction resulting in a (supra-) additive or even synergistic risk cannot be generally assumed and should thus not be postulated. This is a relevant issue for drug interaction software and the tailoring of its alerts. Based on these findings, warnings for adverse drug interactions should be reserved to drugs with established ('known') or 'conditional' TdP potential whose combination might pose an increased, albeit not necessarily synergistic, risk. Because a risk of arrhythmia-induced admission cannot be attributed to all QT-prolonging drugs, indiscriminate warnings in guidelines, product labels, or electronic prescribing systems should be issued with caution unless clinical evidence for the individual drug combination has been established. Indeed, issuing alerts for all possible combinations of potentially QT-prolonging drugs would yield alerts with high frequency (in the percent range) [61, 62]. While warnings in electronic prescribing systems can contribute to adequate prescribing, poor alert specificity and over-alerting are problems relevant to the acceptance of these systems [63, 64].

This study has limitations inherent to observational studies using routine data. First, drug exposure is not necessarily constant and the assumption that drugs are continuously taken within an exposure period will misclassify intermittent users [65]. Any sophisticated method used to determine drug exposure in claims data suffers from the limitation that actual intake within such periods remains unknown. Second, drug exposure is often sensitive to factors that also modify the outcome of interest (e.g., indication, contraindication, disease severity, and adherence). For example, concurrent prescription of multiple drugs may have been avoided in high-risk patients due to skillful prescribing of their physicians. Third, the risk of ADRs is influenced by other (known or unknown) factors or relevant confounders that are inaccessible in claims data [66–68] (e.g., non-prescription drugs [69]), the exposure to which may change over time. Electrolyte balances, individual repolarization reserve and dispersion, beat-to-beat variability, action potential triangulation, and after-depolarization can also vary over time and thus modulate the propensity of experiencing ventricular arrhythmia as a multifactorial event. All of these confounders are not able to be measured in claims data. Another aspect that is inaccessible in claims data applies to the diagnosis code not specifically addressing drug-induced admissions due to ventricular arrhythmia. In the light of unmeasured or immeasurable covariates, causality assessment is not straightforward but rather uncertain due to potential confounding by a co-medication or co-morbidity. Using case-only designs is therefore a conclusive, and probably the most appropriate methodology in this setting, although it still bears the (indeterminable) potential for having time-varying confounding, albeit this is reduced if observation periods are short. Third, the ICD-10-GM coding system does not distinguish between different kinds of ventricular arrhythmia and, therefore, claims data do not provide evidence on the morphology of the arrhythmia that led to admission of these patients. However, in addition to TdP, other forms of serious ventricular arrhythmia are also frequent in patients with QT prolongation [70], making such a distinction likely to be not particularly important. Fourth, our findings cannot readily be generalized to fatal outcomes in primary care because our conceptual approach was based on incident hospital admissions, thus excluding patients with (sudden cardiac) death before reaching a hospital. Finally, the findings deduced from this study have to be interpreted with caution given the study design which investigated rare events that coincide with only a small number of AZCERT drugs in this outpatient setting.

5 Conclusion

This study clearly confirms existing evidence regarding the general association between exposure to TdP-inducing drugs and hospital admission for ventricular arrhythmia. However, it was not able to detect such a risk for drugs generally prolonging QT that do not induce TdP, thus stressing the usefulness of such a distinction. Similarly, when combinations of TdP-inducing drugs were assessed, there was no evidence of an increased risk relating to the

prescription of combinations of QT-prolonging drugs that have no propensity to TdP, whereas the admission risk of drug combinations with known TdP potential appeared to be additive but likely not supra-additive or synergistic, thus questioning the presence of a true pharmacodynamic interaction. Therefore, this finding suggests that the widely practiced strategy of attributing combination therapies of QT-prolonging drugs as particularly high risk, and even considering many of them to be contraindicated, should be questioned and scrutinized in dedicated studies. Such studies should include substantial patient numbers to enable conclusions to be made based on rigorous evidence, which can possibly only be accomplished in multi-national approaches or by joining large databases.

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Compliance with Ethical Standards

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Ethical Approval In Germany by law, retrospective claims analyses do not require ethics committee approval.

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