



Hydroxyzine Initiation Following Drug Safety Advisories on Cardiac Arrhythmias in the UK and Canada: A Longitudinal Cohort Study

Richard L. Morrow¹ · Barbara Mintzes² · Patrick C. Souverein³ · Christine E. Hallgreen⁴ · Bilal Ahmed¹ · Elizabeth E. Roughead⁵ · Marie L. De Bruin^{3,4} · Sarah Brøgger Kristiansen⁶ · Joel Lexchin⁷ · Anna Kemp-Casey⁵ · Ingrid Sketris⁸ · Dee Mangin⁹ · Sallie-Anne Pearson¹⁰ · Lorri Puil¹¹ · Ruth Lopert¹² · Lisa Bero¹³ · Danijela Gnjidic² · Ameet Sarpatwari¹⁴ · Colin R. Dormuth¹

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Abstract

Introduction Regulatory advisories on hydroxyzine and risk of QT prolongation and Torsade de pointes (TdP) were issued in the UK in April 2015 and Canada in June 2016. We hypothesized patients with risk factors for QT prolongation and TdP, compared with those without risk factors, would be less likely to initiate hydroxyzine in the UK and in British Columbia (BC), Canada, following advisories.

Methods We conducted a longitudinal study with repeated measures, and evaluated hydroxyzine initiation in a UK cohort and a concurrent BC control cohort (April 2013–March 2016) as well as in a BC advisory cohort (June 2014–May 2017).

Results This study included 247,665 patients in the UK cohort, 297,147 patients in the BC control cohort, and 303,653 patients in the BC advisory cohort. Over a 12-month post-advisory period, hydroxyzine initiation decreased by 21% in the UK (rate ratio 0.79, 95% confidence interval 0.66–0.96) relative to the expected level of initiation based on the pre-advisory trend. Hydroxyzine initiation did not change in the BC control cohort or following the Canadian advisory in the BC advisory cohort. The decrease in hydroxyzine initiation in the UK in the 12 months after the advisories was not significantly different for patients with risk factors compared with those without risk factors.

Conclusion Hydroxyzine initiation decreased in the UK, but not in BC, in the 12 months following safety advisories. The decrease in hydroxyzine initiation in the UK was not significantly different for patients with versus without risk factors for QT prolongation and TdP.

Key Points

Regulatory drug safety advisories on hydroxyzine and risk of QT prolongation and Torsade de pointes (TdP) arrhythmias were associated with a decrease in hydroxyzine initiation, relative to the expected level of initiation based on the pre-advisory trend, in the UK but not in British Columbia, Canada.

The decline in hydroxyzine initiation in the UK in the 12 months after the advisories was not significantly different for patients with risk factors for QT prolongation and TdP, compared with patients without these risk factors.

1 Introduction

When new information emerges about drug risks, regulators may issue safety advisories to increase awareness among healthcare professionals and the public [1]. Advisories have been associated with changes in drug use, although the impacts vary [2–5]. While the impact of advisories on health outcomes is of interest, it is challenging to directly study health impacts. Depending on the health outcome, challenges in studying the association between a drug safety advisory and risk of an adverse health outcome might include a lengthy or uncertain period between drug exposure and occurrence or detection of the adverse health outcome, confounding from other influences on health outcomes over time, and a lack of statistical power to detect adverse health outcomes if they are rare. An alternative is to study whether an advisory is associated with changes in prescribing to patients with risk factors for an adverse

✉ Richard L. Morrow
richard.morrow@ubc.ca

Extended author information available on the last page of the article

event, compared with those without risk factors, as changing prescribing to these higher-risk patients might be more likely to have an impact on health outcomes. Various studies have used this approach to study the impact of advisories relating to cardiovascular adverse events among patients at higher risk of these outcomes [6–8].

In late April 2015, a Direct Healthcare Professional Communication (DHPC) on hydroxyzine and risk of QT interval prolongation and Torsade de pointes (TdP) arrhythmias was sent to UK physicians from UCB Pharma and Alliance Pharmaceuticals [9]. Concurrently, the UK Medicines and Healthcare products Regulatory Agency (MHRA) independently issued an advisory on these risks, which was made available on a UK government website [10]. In early June 2016, a similar DHPC was sent to healthcare professionals in Canada from Erfa Canada 2012 Inc, and the same DHPC from the company was posted on Health Canada's website [11]. These adverse effects represent a serious health concern as they may lead to sudden cardiac death [11]. Hydroxyzine is an antihistamine that is commonly used on a short-term basis for treating pruritus and may also be used for the management of anxiety [10, 12]. Advisories in both countries highlighted that patients with certain risk factors were at higher risk of these adverse events [9–11]. The UK advisories warned that hydroxyzine should not be prescribed to patients with significant bradycardia or cardiovascular disease. Similarly, the Canadian advisory stated hydroxyzine was contraindicated for patients with significant bradycardia or a history of cardiac arrhythmias. Concomitant use of QT-prolonging drugs was highlighted as a contraindication in advisories in both countries. The UK advisories advised caution regarding comedication with hydroxyzine and drugs that lower the heart rate or potassium levels, while the Canadian advisory stated that concomitant use of hydroxyzine and cytochrome P450 (CYP) 3A4/5 inhibitors was now contraindicated. Advisories in both countries suggested use in older patients should be avoided. In addition, product labelling was updated in both countries to reflect information contained in the advisories [11, 13].

The advice to prescribers in hydroxyzine advisories issued in the UK and Canada suggests that minimizing hydroxyzine use among patients with risk factors for QT prolongation and TdP arrhythmias could reduce drug-related adverse events. The objective of this study was to determine whether patient risk factors for QT prolongation and TdP modified the effect of hydroxyzine advisories on hydroxyzine initiation in the UK and British Columbia (BC), Canada. Risk factors for QT prolongation and TdP included underlying heart conditions; older age; and recent use of QT-prolonging drugs, CYP3A4/5 inhibitors, drugs that lower the heart rate, or drugs that lower potassium levels. We hypothesized that (1) patients with risk factors for QT prolongation

and TdP, compared with patients without these risk factors, would be less likely to be initiated on hydroxyzine in the UK following the UK advisories and in BC following the Canadian advisory; and (2) patients with risk factors for QT prolongation and TdP, compared with patients without these risk factors, would be equally likely to be initiated on hydroxyzine in BC during a control period following the UK advisories and prior to the Canadian advisory.

2 Methods

2.1 Study Design

This study used a longitudinal cohort study design with repeated measures of predictors and outcomes [7, 14, 15]. Longitudinal studies with repeated measures allow for the study of “change in response over time and factors that influence change” [15]. In our study, this design allowed us to evaluate whether patients with risk factors for QT prolongation and TdP would be less likely to be initiated on hydroxyzine, compared with patients without these risk factors, following drug safety advisories, while accounting for pre-advisory trends of hydroxyzine initiation.

2.2 Data Sources

The data source for the UK analyses was the Clinical Practice Research Datalink (CPRD) Gold, which contained electronic medical record (EMR) data from patients of general practitioners (GPs) who contributed data to the database (approximately 4.5 million patients in mid-2015) [16, 17]. The data source for BC analyses was Population Data BC [18–22], which included administrative health data from most residents of BC (which had a population of 4.8 million in mid-2015). BC data excluded about 4% of the population covered by federally insured drug plans (for eligible Indigenous people, members of the Royal Canadian Mounted Police, members of the military, veterans, refugee claimants, and federal prison inmates) [23]. Data sources in both countries included drug data, outpatient visits, demographic data, and deaths; BC data also included hospital admissions. The CPRD contained information about drugs prescribed by GPs, while BC data contained information about drugs dispensed at community pharmacies. Approval of the study protocol was granted by the Independent Scientific Advisory Committee of the MHRA (protocol 20_000191).

2.3 Study Population

The study involved three cohorts of patients, including a UK cohort, a BC control cohort, and a BC advisory cohort (electronic supplementary material [ESM] Fig. S1). We

studied the impact of hydroxyzine advisories issued in the UK on hydroxyzine initiation in the UK cohort, using a 24-month pre-advisory period and a 12-month post-advisory period. The BC control cohort served as a concurrent control group for the UK analysis, as the Canadian advisory was not issued until over 13 months after the UK advisories (ESM Fig. S1). Additionally, we studied the impact of the Canadian advisory in the BC advisory cohort, which was analyzed separately using a 24-month pre-advisory period and 12-month post-advisory period.

We felt the BC control cohort would be a suitable control group for comparison with the UK cohort for various reasons. Residents of UK and BC have similar access to healthcare through a publicly funded healthcare system. Although a preliminary analysis showed a gradually increasing trend of hydroxyzine initiation in the UK and a gradually decreasing trend of initiation in BC, pre-advisory monthly hydroxyzine initiation trends were stable in both countries and we could control for these trends in our analyses. It was possible that the earlier UK advisories might influence prescribing in Canada, but this influence was expected to be weaker than for countries in closer geographic proximity. Although the administrative data in BC captured only drugs dispensed rather than all prescriptions written, whereas the EMR data in the UK included all drugs prescribed, both of these data sources would largely reflect patterns of prescribing behaviour before and after the drug safety advisories [24].

Analyses included patients with at least one outpatient visit for an indication commonly treated with hydroxyzine (contact dermatitis and other eczema, rash, urticaria, allergy, pruritus, atopic dermatitis, and scabies) [ESM Table S1]. The date of an outpatient visit for one of the indications above was defined as the cohort entry date. Anxiety was not included as a cohort entry-defining indication because a pilot analysis suggested hydroxyzine was not commonly prescribed for this indication. We excluded an outpatient visit if the patient was under 40 years of age on the date of the visit because the advisories pertained to cardiovascular risk, and cardiovascular disease is more prevalent among older patients. We excluded an outpatient visit if a patient lacked 365 days of medical coverage prior to the visit to ensure we had at least 365 days of patient history to define predictors of hydroxyzine initiation. In addition, we excluded an outpatient visit if a patient had been prescribed or dispensed hydroxyzine in the 180 days prior to the visit because we considered these patients to be continuing users of hydroxyzine rather than patients at risk of initiating hydroxyzine. As we considered a patient to be at risk of initiating hydroxyzine each time they visited a physician for one of the indications above, patients could enter the cohort more than once.

For the UK cohort and the BC control cohort, the follow-up period was 1 April 2013 to 30 April 2016 (ESM Fig. S1). This included a 24-month pre-advisory period before the

UK advisories were issued (1 April 2013–31 March 2015), a 1-month transition period during April 2015 when the UK advisories were issued, and a 12-month post-advisory period (1 May 2015–30 April 2016). For the BC advisory cohort, the follow-up period was 1 June 2014–30 June 2017. This included a 24-month pre-advisory period (1 June 2014–31 May 2016), a transition period during June 2016 when the Canadian advisory was issued, and a 12-month post-advisory period from 1 July 2016 to 30 June 2017. The BC control and advisory cohorts were the same for the overlapping period of 1 June 2014–30 April 2016, but these cohorts were analyzed separately.

2.4 Predictors of Hydroxyzine Initiation

We specified several predictors of hydroxyzine initiation in our analysis, including medical history variables, medication use variables, and demographic characteristics. The main predictors of interest were risk factors for QT prolongation and TdP highlighted in drug safety advisories, including underlying heart conditions; older age (55–65 years or > 65 years); and recent use of QT-prolonging drugs, CYP3A4/5 inhibitors, drugs that lower the heart rate, or drugs that lower potassium levels. While female sex, renal impairment, and hepatic impairment were not highlighted by the hydroxyzine advisories, we included these as predictors because they are considered to be risk factors for QT prolongation and might influence hydroxyzine initiation [25–31].

Medical history variables were defined based on physician visit records prior to the cohort entry date, including variables for underlying heart conditions, renal impairment, and hepatic impairment (ESM Tables S2–S4). Records of hospital admissions prior to cohort entry were also used to define medical history variables in the BC cohorts, but not in the UK cohort because we lacked linkage to hospital admissions in the UK. Conditions defining the composite variable for underlying heart conditions included cardiac arrhythmias, cardiomyopathy, conduction disorders, heart failure, ischaemic heart disease, insertion of pacemaker or defibrillator, left ventricular hypertrophy, and valvular heart disease [25–32]. We used a 3-year look-back period from a patient's cohort entry date to define medical history variables for the BC cohorts. In the UK cohort, this approach resulted in a much lower prevalence of medical conditions compared with the BC cohorts. As we believed this lower prevalence primarily reflected less recording of chronic conditions in physician visit data in the CPRD, we adopted the approach of defining medical history variables for the UK cohort by assessing these variables based on all data available prior to a patient's cohort entry date rather than a look-back period of 3 years. While we could not adopt the same approach in the BC cohorts (because our BC data extract was limited to a 3-year look-back period), this longer

UK look-back period appeared to result in more consistent identification of relevant medical conditions across the two jurisdictions (see Sect. 2.6 regarding a sensitivity analysis on look-back periods).

Medication use variables included recent use of QT-prolonging drugs with known risk of TdP [33], QT-prolonging drugs with possible risk of TdP, CYP3A4/5 inhibitors [34–38], drugs that lower potassium [39–41], and drugs that lower the heart rate (ESM Tables S5–S9) [42–44]. A patient was defined as having recently used a drug if they had been prescribed or dispensed a drug in the 90 days prior to cohort entry date (7 days prior to cohort entry date for anti-infective drugs included in any of these drug groups, as anti-infectives are typically used for short periods of time).

2.5 Statistical Analysis

A patient was defined as having initiated hydroxyzine if they had been prescribed or dispensed hydroxyzine on their cohort entry date (i.e., the date of an outpatient visit for an indication commonly treated with hydroxyzine) or within 7 days subsequent to this date. We defined hydroxyzine initiation based on prescriptions written or dispensed within 7 days of the outpatient visit because we believed most patients would fill their prescription within this time window and prescriptions filled after this time might not relate to an outpatient visit for one of the cohort-defining indications listed in Sect. 2.3. Follow-up for an observation was ended prior to 7 days after an outpatient visit if any of the following occurred during that time: a prescription for hydroxyzine was written or dispensed to the patient, the patient had a subsequent outpatient visit for an indication commonly treated with hydroxyzine, the patient's medical coverage ended, or the patient died. The dependent variable in all statistical models was a binary variable indicating whether a patient initiated use of hydroxyzine.

We calculated crude monthly hydroxyzine initiation rates as the monthly number of hydroxyzine starts per person-year of follow-up time for each month of the study. Crude monthly hydroxyzine initiation rates were plotted for the UK cohort and the BC control cohort over 37 months of follow-up, including the 24-month pre-advisory period, the 1-month transition period, and the 12-month post-advisory period. Crude monthly initiation rates were also plotted for the UK cohort and the BC advisory cohort over 48 months of follow-up, which showed the 12-month post-advisory period used for the main analysis and the 23-month post-advisory period used in a sensitivity analysis. Similarly, we calculated crude pre-advisory hydroxyzine initiation rates as the number of hydroxyzine starts per person-year of follow-up time during April 2013–March 2015 (for the UK cohort and the

BC control cohort) and during June 2014–May 2016 (for the BC advisory cohort).

Statistical models included an intercept, a monthly trend variable, an indicator for the transition period, an indicator for the post-advisory period, binary predictor variables, and interaction terms for the interaction between the post-advisory period and each predictor variable. We used generalized linear models with a log-link function, a Poisson error distribution, and an autoregressive correlation structure for estimation [45]. Regression models used generalized estimating equations to adjust for clustering effects due to multiple observations for the same patients [46]. Analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Our regression models estimated log rate ratios (RRs) and standard errors, which we converted to RRs and 95% confidence intervals (CIs). Model estimates included RRs for the baseline monthly trend in hydroxyzine initiation, the impact of the transition period on hydroxyzine initiation, and the impact of the advisory on hydroxyzine initiation for patients without the risk factors. RR estimates derived from binary predictor variables represented the association of each risk factor with hydroxyzine initiation prior to the advisories. RR estimates derived from the interaction terms for the interaction between the post-advisory period and each predictor variable represented the impact of risk factors on the effect of an advisory on hydroxyzine initiation (effect modification). RR estimates derived from both the estimated impact of the advisory for patients without risk factors and the estimated effect modification from a given risk factor represented the impact of an advisory for a specific risk group (e.g., patients with underlying heart conditions).

2.6 Secondary and Sensitivity Analyses

As the hydroxyzine advisories highlighted bradycardia and other arrhythmias as risk factors [9–11], we conducted a secondary analysis to analyze the impact of advisories on hydroxyzine initiation for patients with a history of arrhythmias. We conducted a sensitivity analysis using a post-advisory period of 23 months rather than 12 months to analyze the longer-term impacts of the UK and BC advisories. To test whether the UK results were altered by our change in approach for defining medical history variables in the UK cohort (i.e., assessing these variables based on all available data prior to cohort entry), we conducted a sensitivity analysis estimating the impact of the UK advisories on hydroxyzine initiation with medical history variables defined using a 3-year look-back period as initially planned. We conducted a sensitivity analysis in which we evaluated hydroxyzine initiation using a window of 30 days from cohort entry rather than 7 days. Similarly, we estimated models with medication

use variables defined with the look-back period changed from 90 days (7 days for anti-infectives) to 30 days (7 days for anti-infectives), 60 days (7 days for anti-infectives), and 120 days (14 days for anti-infectives).

3 Results

Our identification of patients who met the study eligibility criteria resulted in 247,665 patients in the UK cohort, 297,147 patients in the BC control cohort, and 303,653 patients in the BC advisory cohort (not counting multiple observations per patient) (Fig. 1). Women represented 58–59% of UK and BC patients in the study, while 60–64% of patients were 55 years of age or older in each of the study cohorts (Table 1). The proportion of patients identified as having underlying heart conditions was 17% in the UK cohort, 22% in the BC control cohort, and 23% in the BC advisory cohort. The proportion of patients with recent use of QT-prolonging medications with known risk of TdP was 7–8% in all cohorts.

In the UK cohort, the crude rate of hydroxyzine initiation was gradually increasing during the 24 months prior to the UK advisories, but following the advisories, the rate of hydroxyzine initiation dropped steeply before resuming an increasing trend (Fig. 2). In contrast, the crude rate of hydroxyzine initiation in the BC control cohort was gradually decreasing prior to the UK advisories, and showed little change in the 12 months following the advisories (Fig. 2). Crude rates of hydroxyzine initiation before and after the UK and Canadian advisories are compared in Fig. 3, which shows both the 12-month post-advisory period used for the main analysis and the 23-month post-advisory period used in a sensitivity analysis. The figure suggests the UK hydroxyzine advisories were followed by an immediate drop in hydroxyzine initiation followed by the resumption of an increasing trend, while the Canadian advisory does not appear to be followed by a change in level or trend of hydroxyzine initiation.

3.1 Association of Patient Risk Factors with Initiation Prior to the Advisories

Crude hydroxyzine initiation rates during the 24 months prior to the UK advisories (for the UK cohort and the BC control cohort) and during the 24 months prior to the Canadian advisory (for the BC advisory cohort) are shown in ESM Table S10. Prior to the UK advisories, the rate of hydroxyzine initiation in the UK was 0.84 starts per person-year for patients with underlying heart conditions and 0.80 starts per person-year for patients with recent use of QT-prolonging drugs. Rates of hydroxyzine initiation were higher during the same period in BC, at 1.19 starts per person-year

for patients with underlying heart conditions and 1.20 starts per person-year for patients with recent use of QT-prolonging drugs (ESM Table S10) [rates could exceed one start per person-year because they were based on follow-up on the date of a physician visit for a condition commonly treated with hydroxyzine and up to 7 days following the visit, rather than a full year of follow-up for each patient].

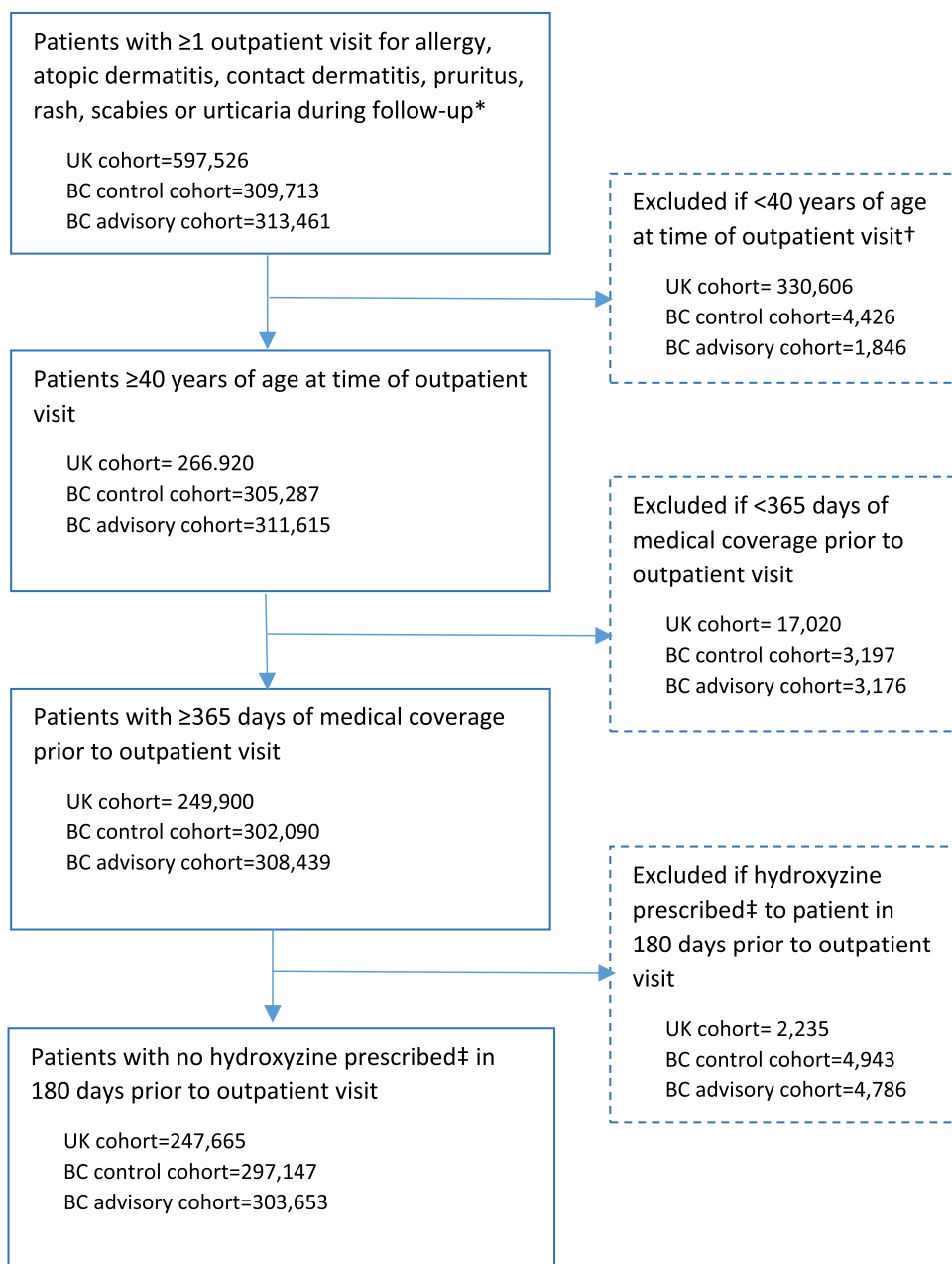
Adjusted estimates of the association of patient risk factors for QT prolongation and TdP with hydroxyzine initiation prior to the advisories are reported in ESM Table S11. Women, compared with men, and patients over 65 years of age, compared with patients aged 40–54 years, were more likely to be initiated on hydroxyzine in all cohorts prior to the advisories. Patients with underlying heart conditions were more likely to be prescribed hydroxyzine in the UK cohort (RR 1.11, 95% CI 1.01–1.22) compared with patients without heart conditions, but less likely to be prescribed hydroxyzine in the BC control cohort (RR 0.89, 95% CI 0.84–0.95) or BC advisory cohort (RR 0.93, 95% CI 0.87–0.98). Similarly, patients with recent use of QT-prolonging drugs with known risk of TdP were more likely to be prescribed hydroxyzine than patients without recent use of these drugs in the UK, but not in BC.

3.2 Impact of Advisories on Hydroxyzine Initiation by Risk Group

The UK advisories were associated with a decline in hydroxyzine initiation of approximately 21% among patients without risk factors for QT prolongation and TdP in the UK cohort (RR 0.79, 95% CI 0.66–0.96) relative to the expected level of hydroxyzine initiation based on the pre-advisory trend, while there was no concurrent change in hydroxyzine initiation in the BC control cohort (Table 2). In the BC advisory cohort, hydroxyzine initiation did not change during the 12-month post-advisory period among patients without risk factors, although initiation dropped temporarily during the month of the advisory (RR 0.82, 95% CI 0.72–0.93).

In the UK cohort, hydroxyzine initiation declined during the 12 months following the UK advisories among patients 55 years of age or older, patients with underlying heart conditions or renal impairment, and patients with recent use of QT-prolonging drugs with known risk of TdP or drugs that lower the heart rate (see part b of Table 2). Hydroxyzine initiation did not change for patients in these risk groups in the BC control cohort during the same period or for patients in these risk groups in the BC advisory cohort following the Canadian advisory. While the UK advisories were associated with a decline in hydroxyzine initiation in the UK cohort among some groups of patients at higher risk, our estimates of whether these risk factors modified the effect of the advisory were non-significant (see part c of Table 2). In effect, there was no statistically significant difference between the

Fig. 1 Selection of study cohorts. *Patients with an outpatient visit for allergy, atopic dermatitis, contact dermatitis, pruritus, rash, scabies or urticaria during follow-up were eligible to be included in the study. The follow-up periods were 1 April 2013 to 30 April 2016 for the UK cohort and BC control cohort, and 1 June 2014 to 30 June 2017 for the BC advisory cohort. †Most patients < 40 years of age were excluded from the BC data extract prior to analysis; any patients < 40 years of age not excluded from the BC data extract were excluded during the selection of study cohorts. ‡Date of prescription was used for the UK cohort and dispensing date was used for the BC control and advisory cohorts. BC British Columbia, UK United Kingdom



decline in hydroxyzine initiation for patients with these risk factors and the decline in initiation for patients without these risk factors in the 12 months following the advisories.

In a secondary analysis, we did not find a significant decrease in hydroxyzine initiation following the UK advisories among patients with a history of cardiac arrhythmias in the UK cohort or the BC control cohort, nor was there a decrease in initiation among this group of patients in the BC advisory cohort following the Canadian advisory (Table 2). Our sensitivity analysis of the impact of advisories on hydroxyzine initiation over a 23-month post-advisory period indicated initiation declined for several risk groups in the UK cohort, but none in the BC advisory

cohort, consistent with our analysis over a 12-month post-advisory period (see part b of Table 3). Over the 23-month post-advisory period, hydroxyzine initiation in the UK cohort declined for patients with underlying heart conditions by about one-third (RR 0.63, 95% CI 0.50–0.80) and for patients with recent use of QT-prolonging drugs with known TdP risk by close to one-half (RR 0.54, 95% CI 0.41–0.71), compared with one-quarter (RR 0.76, 95% CI 0.64–0.89) for patients without risk factors. These two risk factors significantly modified the effect of the advisory over a 23-month post-advisory period (see part c of Table 3).

Table 1 Patient characteristics

Characteristic	UK cohort [<i>n</i> = 247,665] ^a	BC control cohort [<i>n</i> = 297,147] ^a	BC advisory cohort [<i>n</i> = 303,653] ^a
(a) Demographic characteristics			
Female	143,598 (58.0)	175,921 (59.2)	180,055 (59.3)
Male	104,067 (42.0)	121,226 (40.8)	123,598 (40.7)
Age 40–54 years	88,053 (35.6)	118,104 (39.7)	117,243 (38.6)
Age 55–65 years	59,849 (24.2)	81,587 (27.5)	83,450 (27.5)
Age > 65 years	99,763 (40.3)	97,456 (32.8)	102,960 (33.9)
(b) Medical history^b			
Underlying heart conditions (composite)	43,086 (17.4)	66,042 (22.2)	69,379 (22.8)
Ischaemic heart disease	23,132 (9.3)	39,168 (13.2)	40,604 (13.4)
Cardiac arrhythmias	19,658 (7.9)	35,730 (12.0)	38,573 (12.7)
Cardiomyopathy	921 (0.4)	1986 (0.7)	2158 (0.7)
Conduction disorders	1963 (0.8)	3311 (1.1)	3384 (1.1)
Heart failure	5969 (2.4)	14,672 (4.9)	15,167 (5.0)
Insertion of pacemaker or defibrillator	1945 (0.8)	1747 (0.6)	1708 (0.6)
Left ventricular hypertrophy	2358 (1.0)	153 (0.1)	165 (0.1)
Valvular heart disease	5875 (2.4)	3766 (1.3)	4150 (1.4)
Renal impairment	27,838 (11.2)	19,784 (6.7)	21,184 (7.0)
Hepatic impairment	5431 (2.2)	11,167 (3.8)	11,842 (3.9)
(c) Medication use^c			
QT-prolonging drugs, known TdP risk	19,302 (7.8)	21,080 (7.1)	21,501 (7.1)
QT-prolonging drugs, possible TdP risk	22,566 (9.1)	19,285 (6.5)	20,401 (6.7)
CYP3A4/5 inhibitors	5919 (2.4)	7307 (2.5)	7199 (2.4)
Drugs that lower potassium	70,342 (28.4)	61,312 (20.6)	62,632 (20.6)
Drugs that lower the heart rate	36,226 (14.6)	29,881 (10.1)	30,531 (10.1)

Data are expressed as *n* (%)

UK United Kingdom, BC British Columbia, TdP Torsade de pointes, CYP cytochrome P450

^aPatient characteristics were assessed prior to the first instance on which the patient entered a given cohort

^bMedical history characteristics were defined based on diagnoses in the 3 years prior to cohort entry for BC cohorts and on all previous diagnoses for the UK cohort (see sect. 2.4 regarding look-back periods)

^cMedication use was defined based on drugs prescribed or dispensed in the 90 days prior to cohort entry (7 days for anti-infectives)

In a sensitivity analysis using a definition of hydroxyzine initiation evaluated within 30 days of cohort entry, our findings were similar to those using a window of 7 days from cohort entry to define initiation, although decreases in hydroxyzine initiation for risk groups in the UK cohort were slightly attenuated and, in some cases, non-significant (ESM Table S12) When medical history variables were defined using a 3-year look-back period in the UK analysis, model estimates were consistent with the results of analyses that used all available data prior to cohort entry to define medical history variables (ESM Table S13). When the look-back period used to define recent medication use was varied in a sensitivity analysis, use of QT-prolonging drugs with known risk of TdP continued to be associated with a post-advisory decline in hydroxyzine initiation in the UK, but we found that use of drugs that lower the heart rate was no longer significantly associated with a post-advisory decline

in initiation in the UK (ESM Table S14). Our findings for the BC cohorts did not change based on varying look-back periods to define medication use.

4 Discussion

In the UK, drug safety advisories on hydroxyzine and risk of QT prolongation and TdP were associated with a decline in hydroxyzine initiation of approximately 21% in the 12 months after the advisories among patients who had recently visited a physician for contact dermatitis and other eczema, rash, urticaria, allergy, pruritus, atopic dermatitis, or scabies. Our analysis indicated that hydroxyzine initiation did not change among similar patients in BC following a similar Canadian advisory, although hydroxyzine initiation was declining in BC prior to the UK and Canadian advisories,

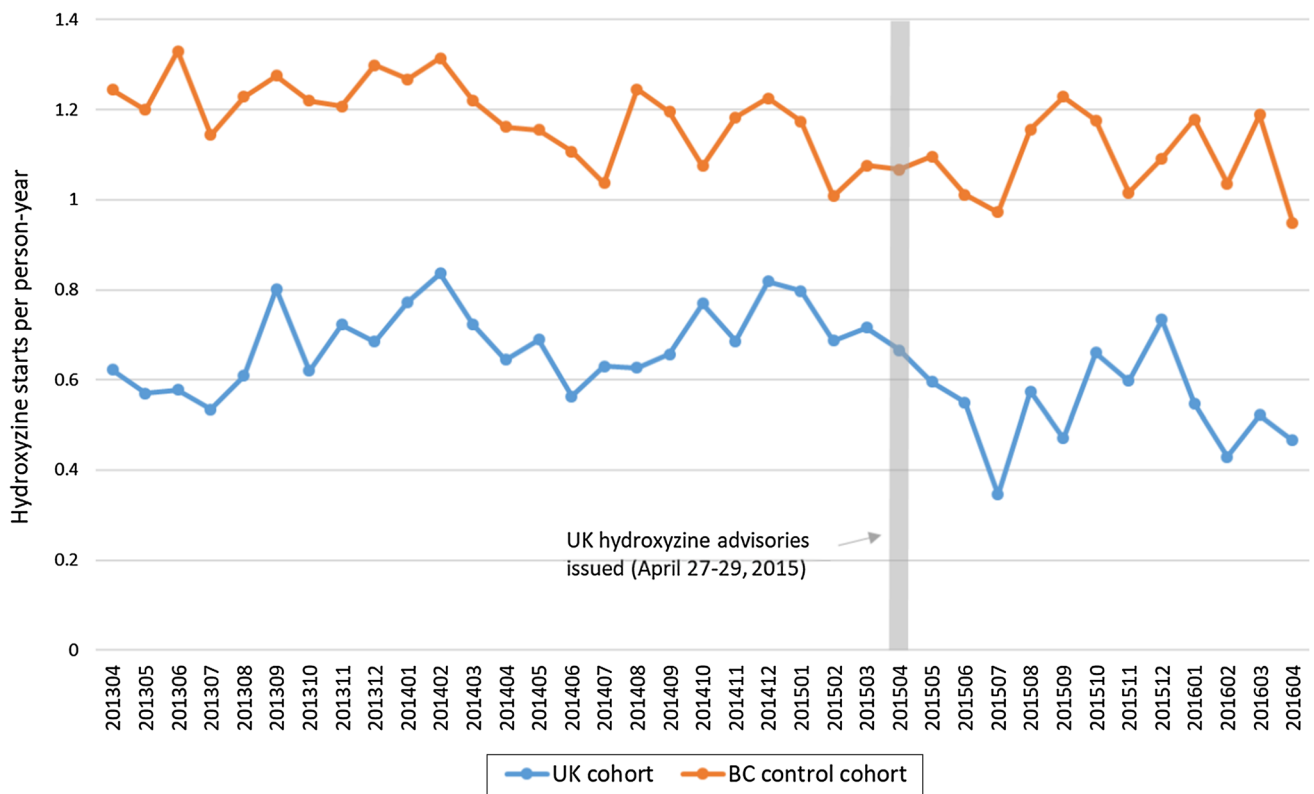


Fig. 2 Crude monthly hydroxyzine initiation rates in the UK following hydroxyzine advisories* versus the BC control cohort. *Hydroxyzine advisories regarding QT prolongation and risk of Torsade de pointes were issued in the UK during 27–29 April 2015. No similar advisory was issued in Canada until 6 June 2016 (after the follow-up period for the BC control cohort had ended). Person-year rates

may exceed 1 hydroxyzine start per year because rates are based on follow-up on the date of a physician visit (for a condition commonly treated with hydroxyzine) and up to 7 days following the visit, rather than a full year of follow-up for each patient. *BC* British Columbia, *UK* United Kingdom

and this might have attenuated an observable association between the Canadian advisory and hydroxyzine initiation in BC. We did not find a statistically significant difference in the reduction of hydroxyzine initiation in the 12 months following the UK advisories for patients with risk factors for QT prolongation and TdP compared with patients without these risk factors.

Physicians in the UK responded to emerging risk information by initiating fewer patients on hydroxyzine, and a sensitivity analysis using a longer post-advisory period suggests they may have adjusted their prescribing based on certain patient risk factors highlighted in the advisories. In this sensitivity analysis, we found hydroxyzine initiation declined in the 23 months following the UK advisories by about one-third among patients with underlying heart conditions and close to one-half among patients with recent use of QT-prolonging drugs with known TdP risk, compared with only one-quarter for patients without risk factors for QT prolongation or TdP. While these results may be considered exploratory, our finding that effect modification was significant for these two risk factors but not other risk

factors related to medical history or recent medication use may reflect the content of the UK advisories. Although renal impairment and hepatic impairment are risk factors for QT prolongation, these were not mentioned in the UK advisories as risk factors related to the use of hydroxyzine. The UK advisories stated that concomitant use of hydroxyzine and other drugs that prolong the QT interval was contraindicated but only advised caution about concomitant use of hydroxyzine and drugs that lower the potassium levels or drugs that lower the heart rate, and unlike the Canadian advisory, they did not warn against concomitant use of hydroxyzine and CYP3A4/5 inhibitors.

4.1 Comparison with Other Studies

Our research builds on findings from a previous study about the impact of the UK hydroxyzine advisories and label changes in England and Scotland and the impact of similar advisories and label changes in Denmark and The Netherlands [47]. Using an interrupted time-series analysis design, the study found hydroxyzine initiation declined in

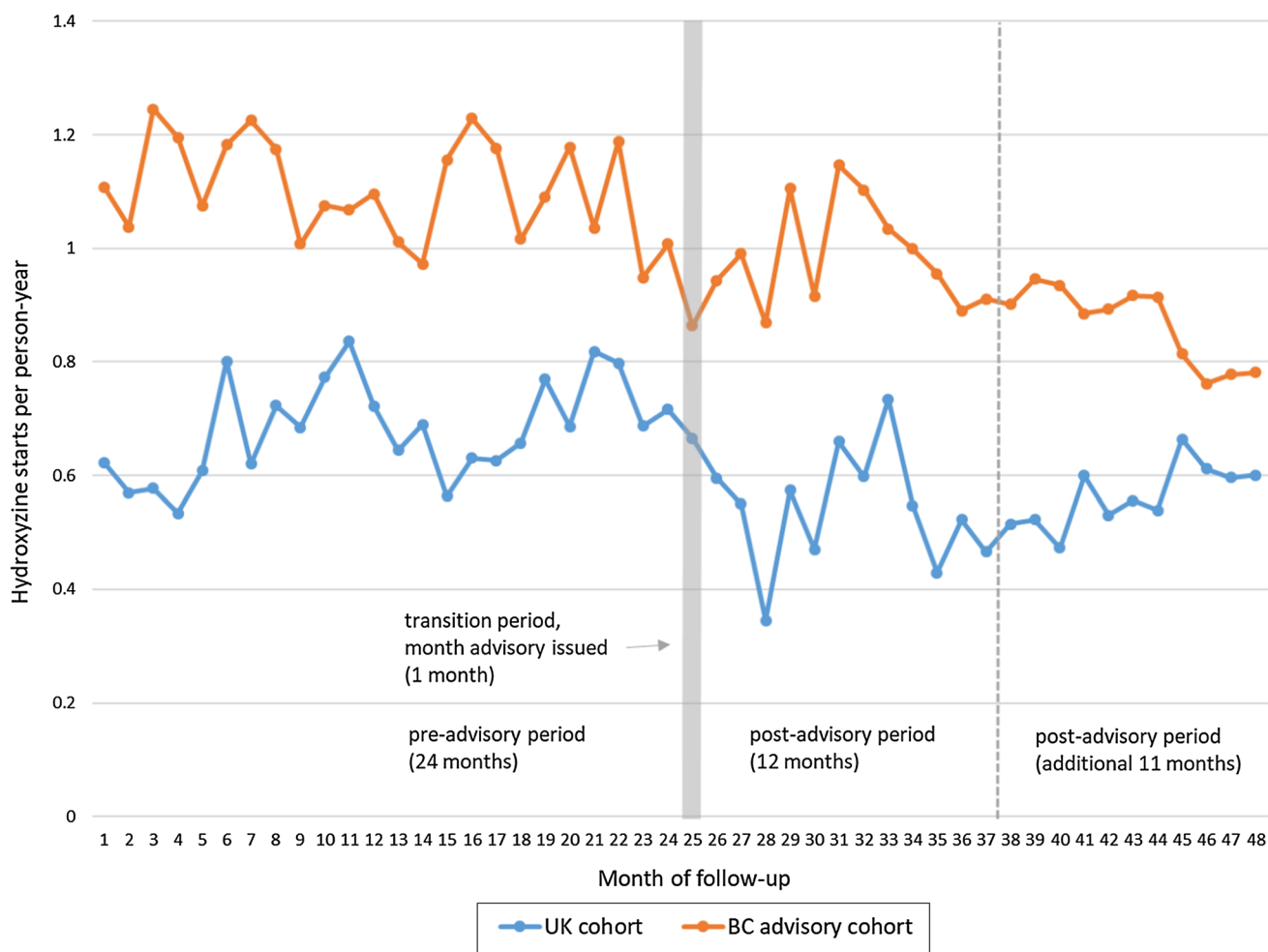


Fig. 3 Crude monthly hydroxyzine initiation rates in the UK cohort versus the BC advisory cohort* showing the 12-month post-advisory period (main analysis) and the 23-month post-advisory period (sensitivity analysis). *Hydroxyzine advisories were issued in the UK during 27–29 April 2015, and a hydroxyzine advisory was issued in Canada on 6 June 2016. Time in this graph represents follow-up time starting 24 months prior to each advisory, rather than calendar

time (the UK and Canadian advisories were not concurrent). Person-year rates may exceed 1 hydroxyzine start per year because rates are based on follow-up on the date of a physician visit (for a condition commonly treated with hydroxyzine) and up to 7 days following the visit, rather than a full year of follow-up for each patient. *BC* British Columbia, *UK* United Kingdom

England and Scotland among patients with cardiovascular disease and patients with use of QT-prolonging drugs during a post-advisory period from early 2015 to 2018. No change in hydroxyzine initiation occurred in The Netherlands among these higher-risk patients over the same period, but the trend in hydroxyzine initiation declined in Denmark among patients with use of QT-prolonging drugs. Consistent with these findings, our study indicated hydroxyzine initiation declined in the UK among patients with underlying heart conditions and recent use of QT-prolonging drugs with known risk of TdP over a 12-month post-advisory period (in our primary analysis) or a 23-month post-advisory period (in a sensitivity analysis).

Our study differed from the earlier study of hydroxyzine advisories discussed above, in two important ways. First,

we estimated the association of advisories with hydroxyzine initiation for patients without risk factors for QT prolongation and TdP, and second, we estimated whether risk factors for QT prolongation and TdP modified the effect of the UK advisory on hydroxyzine initiation. Our finding that hydroxyzine initiation declined 21% for patients without risk factors for QT prolongation and TdP appears to indicate that UK physicians felt the risk of adverse events highlighted by the advisories were relevant to all patients rather than only to higher-risk patients and they changed their prescribing accordingly. This finding may reflect the content of the MHRA advisory, which states that a review “concluded that hydroxyzine is associated with a small risk of QT interval prolongation and Torsade de Pointes” [10]. While the advisory highlighted that “events are most likely to occur

Table 2 Association of regulatory drug safety advisories with hydroxyzine initiation

Variable	Association with hydroxyzine initiation		
	UK cohort [n = 247,665]	BC control cohort [n = 297,147]	BC advisory cohort [n = 303,653]
(a) Trend and time period			
Monthly trend	1.01 (1.00–1.01)	0.99 (0.99–1.00)	1.00 (0.99–1.00)
Impact of transition period	0.89 (0.74–1.08)	0.94 (0.84–1.06)	0.82 (0.72–0.93)
Impact of advisory ^a	0.79 (0.66–0.96)	0.99 (0.89–1.10)	0.99 (0.89–1.10)
(b) Association of advisory with initiation by risk group^{b,c}			
Female	0.83 (0.65–1.05)	0.96 (0.84–1.09)	0.90 (0.79–1.03)
Age 55–65 years	0.67 (0.51–0.88)	0.99 (0.86–1.15)	0.97 (0.84–1.13)
Age >65 years	0.68 (0.52–0.88)	0.98 (0.85–1.13)	0.98 (0.85–1.14)
Underlying heart conditions (composite)	0.69 (0.52–0.91)	1.06 (0.91–1.22)	0.97 (0.84–1.13)
Renal impairment	0.71 (0.54–0.95)	1.02 (0.86–1.23)	1.04 (0.87–1.25)
Hepatic impairment	0.77 (0.48–1.23)	1.12 (0.91–1.38)	0.97 (0.78–1.21)
QT-prolonging drugs, known risk of TdP	0.65 (0.47–0.90)	1.02 (0.85–1.22)	1.07 (0.89–1.29)
QT-prolonging drugs, possible risk of TdP	0.83 (0.62–1.11)	1.01 (0.84–1.21)	1.05 (0.87–1.27)
CYP3A4/5 inhibitors	0.67 (0.41–1.12)	1.25 (0.96–1.63)	0.93 (0.71–1.23)
Drugs that lower potassium	0.81 (0.63–1.03)	1.00 (0.87–1.14)	1.03 (0.90–1.19)
Drugs that lower the heart rate	0.73 (0.54–0.99)	1.00 (0.84–1.19)	10.4 (0.87–1.24)
(c) Association of risk factors with effect of advisory on initiation (effect modification)^{c,d}			
Female	1.04 (0.90–1.20)	0.97 (0.90–1.05)	0.91 (0.84–0.99)
Age 55–65 years	0.84 (0.68–1.03)	1.01 (0.91–1.11)	0.98 (0.89–1.09)
Age >65 years	0.85 (0.71–1.02)	0.99 (0.90–1.10)	0.99 (0.90–1.10)
Underlying heart conditions (composite)	0.86 (0.70–1.07)	1.07 (0.97–1.19)	0.98 (0.88–1.09)
Renal impairment	0.90 (0.72–1.12)	1.04 (0.89–1.20)	1.06 (0.91–1.22)
Hepatic impairment	0.97 (0.63–1.49)	1.13 (0.94–1.36)	0.99 (0.81–1.19)
QT-prolonging drugs, known risk of TdP	0.82 (0.63–1.07)	1.03 (0.89–1.20)	1.09 (0.93–1.26)
QT-prolonging drugs, possible risk of TdP	1.05 (0.84–1.31)	1.02 (0.87–1.19)	1.06 (0.91–1.24)
CYP3A4/5 inhibitors	0.85 (0.53–1.36)	1.26 (0.99–1.61)	0.95 (0.73–1.22)
Drugs that lower potassium	1.02 (0.87–1.19)	1.01 (0.92–1.10)	1.04 (0.95–1.14)
Drugs that lower the heart rate	0.92 (0.73–1.16)	1.01 (0.88–1.16)	1.05 (0.91–1.21)
(d) Association of advisory with initiation (secondary analysis)^b			
Cardiac arrhythmias	0.75 (0.54–1.03)	0.99 (0.84–1.16)	0.95 (0.81–1.12)

Data are expressed as RR (95% CI)

CI confidence interval, UK United Kingdom, BC British Columbia, TdP Torsade de pointes, CYP cytochrome P450, RR rate ratio

^a Association of advisory with initiation for patients without risk factors listed in part (b)^b Association of advisory with initiation for patients with a given risk factor^c The referent group for female is male, and the referent group for age 55–65 years and age >65 years is age 40–54 years^d Represents association of advisory with initiation for patients with a given risk factor, beyond the advisory impact shown in part (a)

Table 3 Association of regulatory advisories with hydroxyzine initiation (sensitivity analysis with 23-month post-advisory period)

Patient group	Association with hydroxyzine initiation	
	UK cohort [<i>n</i> = 284,944]	BC advisory cohort [<i>n</i> = 377,584]
(a) Trend and time period		
Monthly trend	1.01 (1.00–1.01)	0.99 (0.99–1.00)
Impact of transition period	0.89 (0.73–1.07)	0.85 (0.75–0.97)
Impact of advisory ^a	0.76 (0.64–0.89)	1.02 (0.93–1.12)
(b) Association of advisory with initiation by risk group ^{b,c}		
Female	0.79 (0.64–0.97)	0.94 (0.84–1.06)
Age 55–65 years	0.65 (0.51–0.83)	1.03 (0.90–1.17)
Age > 65 years	0.67 (0.53–0.84)	1.04 (0.91–1.18)
Underlying heart conditions (composite)	0.63 (0.50–0.80)	0.98 (0.86–1.12)
Renal impairment	0.72 (0.56–0.91)	1.09 (0.93–1.27)
Hepatic impairment	0.73 (0.50–1.06)	1.04 (0.86–1.25)
QT-prolonging drugs, known risk of TdP	0.54 (0.41–0.71)	1.10 (0.94–1.29)
QT-prolonging drugs, possible risk of TdP	0.73 (0.57–0.94)	1.11 (0.94–1.30)
CYP3A4/5 inhibitors	0.59 (0.39–0.90)	0.94 (0.74–1.18)
Drugs that lower potassium	0.79 (0.64–0.98)	1.02 (0.90–1.15)
Drugs that lower the heart rate	0.74 (0.58–0.95)	1.04 (0.89–1.21)
(c) Association of risk factors with effect of advisory on initiation (effect modification) ^{c,d}		
Female	1.05 (0.93–1.18)	0.92 (0.86–0.99)
Age 55–65 years	0.86 (0.73–1.02)	1.01 (0.92–1.10)
Age >65 years	0.88 (0.76–1.03)	1.02 (0.93–1.11)
Underlying heart conditions (composite)	0.83 (0.70–0.99)	0.96 (0.88–1.05)
Renal impairment	0.95 (0.79–1.13)	1.07 (0.94–1.21)
Hepatic impairment	0.96 (0.68–1.35)	1.02 (0.87–1.19)
QT-prolonging drugs, known risk of TdP	0.71 (0.57–0.89)	1.08 (0.95–1.23)
QT-prolonging drugs, possible risk of TdP	0.97 (0.80–1.17)	1.08 (0.95–1.24)
CYP3A4/5 inhibitors	0.78 (0.53–1.16)	0.92 (0.74–1.14)
Drugs that lower potassium	1.05 (0.92–1.20)	1.00 (0.92–1.08)
Drugs that lower the heart rate	0.98 (0.82–1.19)	1.02 (0.90–1.14)

Data are expressed as RR (95% CI)

CI confidence interval, UK United Kingdom, BC British Columbia, RR rate ratio, TdP Torsade de pointes

^aAssociation of advisory with initiation for patients without risk factors listed in part (b)

^bAssociation of advisory with initiation for patients with a given risk factor

^cThe referent group for female is male, and the referent group for age 55–65 years and age > 65 years is age 40–54 years

^dRepresents association of advisory with initiation for patients with a given risk factor, beyond the advisory impact shown in part (a)

in patients who already have risk factors for QT prolongation”, the risk information presented is not restricted to such patients [10]. Although we did not find a statistically significant effect modification in the 12 months following the UK advisories, our sensitivity analysis with a 23-month post-advisory period suggested that hydroxyzine initiation declined to a greater extent for patients with underlying heart conditions or recent use of QT-prolonging drugs with known risk of TdP than for other patients. This finding may

indicate that UK physicians adjusted their prescribing based on patient risk factors.

The reasons for the difference in the impact of advisories on hydroxyzine initiation in the UK compared with BC, or other jurisdictions, are unclear. Factors contributing to impact might include pre-existing patterns of clinical practice, the format of advisories, and source of the advisories. In the UK, patients with heart conditions and patients with recent use of QT-prolonging drugs with known risk of TdP were more likely than patients without these risk

factors to be initiated on hydroxyzine prior to the UK advisories, while patients with heart conditions were slightly less likely than patients without heart conditions to be initiated on hydroxyzine in BC prior to the Canadian advisory. However, the pre-advisory rate of hydroxyzine initiation for patients with these risk factors was higher in BC than in the UK, which suggests an opportunity existed for BC physicians to reduce prescribing of hydroxyzine to higher-risk patients in response to the new safety information. Physicians have stated they find concise information about drug safety more useful [48]. They might therefore have valued the shorter format of the MHRA advisory and UK DHPC (containing about 350 and 500 words, respectively), compared with the Canadian DHPC (over 800 words), although all of these advisories contained a short section highlighting key messages [9–11]. While advisories varied somewhat in wording and level of detail, advisories in the UK and Canada contained similar messages. In addition, the DHPCs on hydroxyzine in the UK, Denmark and The Netherlands were similar because they were issued as part of risk minimization measures harmonized across the European Union [13]. While DHPCs were issued in Canada, Denmark, The Netherlands and the UK (and the European Medicines Agency also publicly released recommendations regarding hydroxyzine), the MHRA also issued its own advisory independent of industry [10, 13, 49]. It is possible that the greater change in hydroxyzine initiation in the UK was related to the repetition of risk information in two advisories or the credibility of an independent advisory from a national regulator, as previous research has suggested that physicians are less trusting of risk information from companies [48, 50].

4.2 Policy Implications

Our study has implications for policy on regulatory risk communication. We found that physicians in the UK may have adjusted their prescribing of hydroxyzine according to patient risk factors, which highlights the value of including information about risk factors for drug-related adverse events in advisories when this information is available. Although it remains uncertain whether the source of advisories was associated with their impact on hydroxyzine initiation, it may be valuable for regulators to issue advisories that are independent of industry to provide information to healthcare professionals that is less likely to be perceived as commercially biased. In addition, our study indicated the Canadian advisory had little impact on hydroxyzine initiation in BC, even though it communicated new contraindications, and a similar advisory in the UK led to changes in prescribing. This suggests it is important for regulators to understand reasons why certain advisories have little impact on clinical practice while others are more effective.

4.3 Strengths and Limitations of this Study

A strength of this study was that we not only evaluated the impact of hydroxyzine advisories on hydroxyzine initiation among patients with risk factors for QT prolongation and TdP but also estimated effect modification to determine whether changes in initiation were significantly different for patients with risk factors compared with those without risk factors. As the Canadian advisory was issued more than 13 months after the UK advisories, it was possible to have BC patients serve as a concurrent control group for the UK analysis with a 12-month post-advisory period. Our study also had some limitations. Our analysis with a 12-month post-advisory period had less statistical power than our analysis with a 23-month post-advisory period (due to including 11 fewer months of data), which might in part explain the difference in our findings from these analyses in the UK cohort. Our analysis of advisories may have been subject to confounding from other factors influencing prescribing of hydroxyzine over time. However, we included a BC control cohort in our analysis as a concurrent control group to help identify the presence of time-varying confounding but did not find any statistically significant changes in hydroxyzine initiation in this control cohort during a 12-month post-advisory period. We evaluated whether hydroxyzine initiation was reduced among patients with recent use of QT-prolonging drugs and other drugs that advisories warned should not be used with hydroxyzine. However, it is possible that some patients temporarily suspended use of these drugs while taking hydroxyzine on a short-term basis, which we did not measure but which would also be consistent with advice to avoid concomitant use of hydroxyzine and these drugs.

5 Conclusions

Hydroxyzine initiation decreased in the UK in the 12 months following drug safety advisories regarding the risk of QT prolongation and TdP arrhythmias, but the decrease in initiation was not significantly different for patients with risk factors for QT prolongation and TdP compared with those without risk factors. Hydroxyzine initiation did not change in BC in the 12 months following a similar advisory issued in Canada. It would be valuable for future research to compare and contrast approaches and contexts to explore reasons for differential impacts of similar advisories issued in different jurisdictions.

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Declarations

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Availability of data and material The authors are unable to share data used for this study due to a lack of data permissions for this purpose.

Code availability Programming code is unavailable.

Ethical approval Research ethics board approval was obtained from the University of British Columbia Clinical Research Ethics Board (H20-00929). In addition, the CPRD has received ethics approval from the NHS Health Research Authority to support research using anonymized patient data.

Consent to participate Informed consent was unnecessary as the study used only secondary administrative health data, which had been de-identified prior to data access.

Consent for publication Not applicable.

Author contributions CD and RM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: CD, SP, BM, AK-C, RL, DM, CEH, MLDB, LP, ER, RM, IS, JL, LB, PCS, AS, BA, SBK, and DG. Acquisition, analysis or interpretation of data: CD, SP,

BM, AK-C, RL, DM, CEH, MLDB, LP, ER, RM, IS, JL, LB, PCS, AS, BA, SBK, and DG. Drafting of the manuscript: RM. Critical revision of the manuscript: CD, SP, BM, AK-C, RL, DM, CEH, MLDB, LP, ER, RM, IS, JL, LB, PCS, AS, BA, SBK, and DG. Statistical analysis: CD and RM. Obtaining funding: CD, SP, BM, RL, DM, CEH, MLDB, LP, ER, IS, JL, LB, PCS, AS and DG. Supervision: CD and BM. Final approval of version to be published: CD, SP, BM, AK-C, RL, DM, CEH, MLDB, LP, ER, RM, IS, JL, LB, PCS, AS, BA, SBK, and DG. All authors agree to be accountable to all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Authors and Affiliations

Richard L. Morrow¹  · Barbara Mintzes² · Patrick C. Souverein³ · Christine E. Hallgreen⁴ · Bilal Ahmed¹ · Elizabeth E. Roughead⁵ · Marie L. De Bruin^{3,4} · Sarah Brøgger Kristiansen⁶ · Joel Lexchin⁷ · Anna Kemp-Casey⁵ · Ingrid Sketris⁸ · Dee Mangin⁹ · Sallie-Anne Pearson¹⁰ · Lorri Puil¹¹ · Ruth Lopert¹² · Lisa Bero¹³ · Danijela Gnjidic² · Ameet Sarpatwari¹⁴ · Colin R. Dormuth¹

¹ Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, 210-1110 Government St., Victoria, BC V8W 1Y2, Canada

² Faculty of Medicine and Health and Charles Perkins Centre, School of Pharmacy, University of Sydney, Sydney, NSW, Australia

³ Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

⁴ Department of Pharmacy, Faculty of Health and Medical Sciences, Copenhagen Centre for Regulatory Science, University of Copenhagen, Copenhagen, Denmark

⁵ Clinical and Health Sciences, University of South Australia, Adelaide, SA, Australia

⁶ Department of Drug Design and Pharmacology, Pharmacovigilance Research Center, University of Copenhagen, Copenhagen, Denmark

⁷ Faculty of Health, York University, Toronto, ON, Canada

- ⁸ Department of Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada
- ⁹ Department of Family Medicine, McMaster University, Hamilton, ON, Canada
- ¹⁰ Faculty of Medicine, Centre for Big Data Research in Health, University of New South Wales, Sydney, NSW, Australia
- ¹¹ Faculty of Medicine, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
- ¹² Department of Health Policy and Management, George Washington University, Washington, DC, USA
- ¹³ School of Medicine and Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
- ¹⁴ Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA