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ORIGINAL RESEARCH ARTICLE

Adverse Gastrointestinal Events with Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitors: Nested Case–Control Study

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Abstract

Background Intravenous administration of vascular endothelial growth factor (VEGF)-inhibiting drugs is associated with adverse gastrointestinal (GI) events. Clinical trials of VEGF inhibitors used for the treatment of retinal diseases have suggested higher risks of adverse GI events among patients treated with bevacizumab. However, population-based studies have been lacking.

Objective Our objective was to assess risks for GI adverse events associated with intravitreal injections of VEGF-inhibiting drugs.

Methods We conducted a population-based, nested case–control study of 114,427 older adults in Ontario, Canada, with retinal disease identified between 1 November 2005 and 30 April 2011. Of these, 3,582 cases were admitted to hospital or assessed in an emergency department for GI adverse events. Controls were matched to cases on the basis of age, sex, and outcome history.

Results Patients experiencing adverse events were equally as likely as matched controls to have been exposed to bevacizumab or ranibizumab. Adjusted odds ratios for bevacizumab were 1.05 (95 % confidence interval [CI]

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Key Points

Clinical trials of vascular endothelial growth factor (VEGF)-inhibiting drugs used in the treatment of retinal diseases have suggested higher risks of systemic adverse events among patients receiving bevacizumab, a finding driven by higher risks of adverse gastrointestinal (GI) events

Clinical trials have a number of limitations regarding the assessment of adverse events

Our population-based study suggests that intravitreal injections of bevacizumab and ranibizumab are not associated with increased risks of adverse GI events, and that the two drugs do not impart differing risks of adverse GI outcomes

Our findings complement results from clinical trials and will help to inform clinical decision making and drug policy regarding the adverse event profile and comparative safety of intravitreal VEGF inhibitors

0.69–1.61) for upper GI ulceration, 1.29 (95 % CI 0.86–1.96) for diverticular disease, 1.49 (95 % CI 0.84–2.63) for pancreatitis, 0.82 (95 % CI 0.53–1.29) for cholelithiasis, and 1.45 (95 % CI 0.67–3.12) for cholecystitis. For ranibizumab they were 1.25 (95 % CI 0.88–1.77) for upper GI ulceration, 1.12 (95 % CI 0.83–1.52) for diverticular disease, 0.85 (95 % CI 0.51–1.40) for pancreatitis, 0.77 (95 % CI 0.53–1.11) for cholelithiasis, and 0.83 (95 % CI 0.44–1.56) for cholecystitis. Results were similar when the analysis was restricted to patients only exposed to a single type of VEGF inhibitor.

Conclusions In this population-based study, intravitreal injections of bevacizumab and ranibizumab were not associated with increased risks of adverse GI events.

1 Introduction

The treatment of retinal disease has been revolutionized by the introduction of vascular endothelial growth factor (VEGF) inhibitors [1–6]. However, because VEGF plays an important role in many physiological processes, inhibition of this signaling molecule may cause serious adverse events [7–10]. While the vascular risks associated with intravenous administration of the VEGF inhibitor bevacizumab in the treatment of cancer have been widely publicized, adverse gastrointestinal (GI) and pancreaticobiliary events are also associated with VEGF inhibition in cancer patients [4, 11–19]. Whether this risk of adverse GI events can be extrapolated to the small doses of VEGF inhibitors used in the treatment of eye diseases remains the subject of controversy [20].

The possibility that specific VEGF inhibitors used in the treatment of retinal disease differ in their GI risk profiles has been raised by recent clinical trial results. The CATT (Comparison of Age-Related Macular Degeneration Treatment Trials) and the IVAN (Randomised Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation) trials compared intravitreal bevacizumab versus ranibizumab in the treatment of age-related macular degeneration (AMD) [4, 18, 19]. These trials found lower risks of adverse outcomes among patients receiving ranibizumab, a finding driven primarily by lower risks of adverse GI events (CATT ranibizumab vs. bevacizumab 1-year odds ratio [OR] 0.32, 95 % confidence interval [CI] 0.12–0.89; IVAN ranibizumab vs. bevacizumab OR 0.15, 95 % CI 0.02–1.29). However, clinical trials and meta-analyses have limitations, including poor generalizability to the types of patients who receive treatment in routine clinical practice and a lack of power to detect adverse event risks [21]. Consequently, large population-based observational studies are an important source of information on safety that complement the results of clinical trials [22].

To date, the few population-based studies that have investigated the safety of intravitreal VEGF inhibitors have focused on vascular events such as stroke, myocardial infarction, bleeding, venous thromboembolism, and death [23–27]. Consequently, the risks of adverse GI and pancreaticobiliary events with the use of intravitreal VEGF inhibitors remain unclear. Hence, we carried out a population-based nested case–control study to evaluate these risks.

2 Methods

2.1 Overview

We conducted a population-based, nested case–control study to assess the association of serious GI and pancreaticobiliary adverse events with intravitreal injections of VEGF inhibitors. We used multiple linked healthcare databases to investigate associations between five outcomes pertaining to the upper GI tract, lower GI tract, and pancreaticobiliary systems (upper GI ulceration, diverticular disease, pancreatitis, cholelithiasis, and cholecystitis) and exposure to intravitreal injections of bevacizumab and ranibizumab. Outcomes were chosen based upon primary data from the CATT and IVAN trials. The study protocol was approved by the Research Ethics Board at Queen's University, Kingston, Ontario, Canada (file No. 6004374), adheres to the tenets of the Declaration of Helsinki, and follows the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines for reporting observational studies (http://www.strobe-statement.org/) [28].

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2.2 Data Sources

Universal healthcare insurance is provided to all 13 million residents in the province of Ontario, and the health administrative data derived from the databases utilized are population based. For this study, we linked records from seven databases. The Ontario Health Insurance Plan database contains information on inpatient and outpatient physician services and has been established as having excellent reliability in recording medical procedures [29]. The Ontario Drug Benefit database records all prescriptions provided for patients aged 65 years or older for formulary drugs, with an error rate of less than 1 % [29]. The Canadian Institute for Health Information Discharge Abstract Database provides information on all hospitalizations in Ontario [30]. The National Ambulatory Care Reporting System database records detailed information on all visits to hospital emergency departments [31, 32]. The Registered Persons Database contains demographic information on all residents, and the Ontario Diabetes Database contains validated data regarding Ontario residents with diabetes [33]. The Institute for Clinical Evaluative Sciences Physician Database contains data on all physicians in Ontario. The databases used provide accurate data regarding the variables investigated in this study [29]. Patient confidentiality was maintained via encrypted healthcare identification numbers and strict adherence to privacy protocols.

2.3 Study Population

Using the Ontario Health Insurance Plan Database, and based on a previously published algorithm [25], we identified a base cohort of patients diagnosed as having retinal disease (*International Classification of Disease Ninth Revision* [ICD-9] code 362) within the previous 2 years who were aged 66 years and older between 1 November 2005 and 30 April 2011. To ensure that patients in the cohort could access intravitreal injections if clinically indicated, we limited our analysis to subjects who had seen an ophthalmologist who offered intravitreal injections [25].

2.4 Outcomes and Case Ascertainment

We defined cases as patients who were admitted to hospital or assessed in a hospital emergency department between 1 November 2005 and 30 April 2011 with a primary diagnosis of upper GI ulceration (ICD-10 code K25, K26, K27, K28, or K29), diverticular disease (K57), pancreatitis (K85, K86.0, or K86.1), cholelithiasis (K80), or cholecystitis (K81.0, K81.1, K81.8, or K81.9). The index date was defined as the date of hospital admission or emergency department visit. The positive predictive values for the diagnoses of diverticular disease and cholelithiasis in this database are 87 and 81 %, respectively, compared with direct chart review [30]. Similarly, administrative data coding for upper GI ulceration and pancreatitis were highly predictive of the diagnosis in other validation studies, and the cholecystitis coding used in our study has been used in previous reports [34–37]. For each outcome, we included only the first event in our analysis for patients who experienced multiple occurrences during the study period. Patients experiencing one study outcome remained eligible to be controls for cases who experienced one of the other study outcomes. Control patients remained eligible to experience subsequent outcome events.

2.5 Control Selection and Assessment of Exposures and Covariates

We randomly selected up to five controls (matched according to age, sex, and history of the outcome in the preceding 5 years) for each case and assigned controls the same index date as their respective cases. We used the Ontario Health Insurance Plan and Ontario Drug Benefit databases to identify intravitreal injections of ranibizumab and bevacizumab, as detailed previously [25]. We adjusted for multiple potential confounders. The number of distinct drugs dispensed in the year before the index date was used as a measure of comorbidity [38, 39]. Income was estimated from neighbourhood income quintiles based on Statistics Canada census data. We defined diabetes status on the basis of the validated Ontario diabetes database [33]. We also adjusted for exposure to specific drugs within the year before the index date, grouped by mechanism of action to avoid statistical model over-fitting. Specific comorbidities and procedures (i.e., diabetes, evidence of alcohol use disorder, any cancer, pancreatic cancer, chronic kidney disease, and endoscopic retrograde cholangiopancreatography) were also included in the multivariate models.

2.6 Statistical Analysis

A nested case–control analysis was used to evaluate the association between exposure to intravitreal VEGF inhibitor and each outcome [40, 41]. This analysis provides unbiased estimates of the rate ratios obtained from time-to-event analyses of the full cohort [42–44]. We used conditional logistic regression to estimate ORs for the association between adverse outcomes and exposure to VEGF-inhibitor injections, controlling for potential confounding variables. In our primary analysis, we assessed the risk associated with exposure to bevacizumab or ranibizumab within 180 days before the adverse event. This period was based on the timing of serious adverse

events observed in trials of bevacizumab as a cancer therapy [11]. In a second analysis, to allow for direct comparison between bevacizumab and ranibizumab, we assessed the risk associated with exclusive bevacizumab exposure by using exclusive ranibizumab exposure as the reference. All analyses were carried out at the Institute for Clinical Evaluative Sciences using SAS version 9.2 (Cary, NC, USA).

3 Results

3.1 Baseline Characteristics of Cases and Controls

We identified 114,427 older adults with retinal disease over the study period (Table 1). Within this base cohort, we identified 3,589 cases, 77 of which could not be matched to a control patient. The remaining 3,582 cases, including 908 (0.8 %) cases of upper GI ulceration, 500 (0.4 %) of pancreatitis, 986 (0.9 %) of diverticular disease, 837 (0.7 %) of cholelithiasis, and 351 (0.3 %) of cholecystitis were matched to 17,820 control patients, with 98.7 % of cases matched to five controls each (Table 1). The percentage of patients with diabetes ranged from approximately 21 % (cholecystitis) to approximately 40 % (GI ulceration). As expected, a history of comorbidity, including chronic kidney disease and diabetes mellitus, were more common among patients with adverse outcomes, and recent endoscopic retrograde cholangiopancreatography and cholelithiasis were more common in pancreatitis case patients than in their matched controls (Table 1).

3.2 Association between Upper Gastrointestinal (GI) Ulceration and Vascular Endothelial Growth Factor (VEGF) Inhibitors

In our primary analysis, 48 (5.3 %) of 908 cases with upper GI ulceration and 226 (5.0 %) of 4,535 controls had received ranibizumab in the 180 days before the index date. We found no statistically significant association between upper GI ulceration and exposure to ranibizumab (adjusted OR 1.25; 95 % CI 0.88–1.77; Fig. 1). A total of 31 (3.4 %) of 908 cases with upper GI ulceration and 161 (3.6 %) of 4,535 controls had received bevacizumab in the 180 days before the index date. No significant association existed between upper GI ulceration and exposure to bevacizumab (adjusted OR 1.05; 95 % CI 0.69–1.61; Fig. 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with upper GI ulceration (adjusted OR 0.86; 95 % CI 0.48–1.54; Fig. 2).

3.3 Association between Diverticular Disease and VEGF Inhibitors

In our primary analysis, 62 (6.3 %) of 986 cases with diverticular disease and 278 (5.7 %) of 4,890 controls had received ranibizumab in the 180 days before the index date. We found no statistically significant association between diverticular disease and exposure to ranibizumab (adjusted OR 1.12; 95 % CI 0.83–1.52; Fig. 1). A total of 32 (3.2 %) of 986 cases with diverticular disease and 122 (2.5 %) of 4,890 controls had received bevacizumab in the 180 days before the index date. No significant association existed between diverticular disease and exposure to bevacizumab (adjusted OR 1.29; 95 % CI 0.86–1.96; Fig. 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with diverticular disease (adjusted OR 1.17; 95 % CI 0.69–2.01; Fig. 2).

3.4 Association between Pancreatitis and VEGF Inhibitors

In our primary analysis, 26 (5.2 %) of 500 cases with pancreatitis and 124 (5.0 %) of 2,468 controls had received ranibizumab in the 180 days before the index date. We found no statistically significant association between pancreatitis and exposure to ranibizumab (adjusted OR 0.85; 95 % CI 0.51–1.40; Fig. 1). A total of 17 (3.4 %) of 500 cases with pancreatitis and 70 (2.8 %) of 2,468 controls had received bevacizumab in the 180 days before the index date. No significant association existed between pancreatitis and exposure to bevacizumab (adjusted OR 1.49; 95 % CI 0.84–2.63; Fig. 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with pancreatitis (adjusted OR 1.79; 95 % CI 0.81–3.95; Fig. 2).

3.5 Association between Cholelithiasis and VEGF Inhibitors

In our primary analysis, 36 (4.3 %) of 837 cases with cholelithiasis and 243 (5.8 %) of 4,173 controls had received ranibizumab in the 180 days before the index date. We found no statistically significant association between cholelithiasis and exposure to ranibizumab (adjusted OR 0.77; 95 % CI 0.53–1.11; Fig. 1). A total of 24 (2.9 %) of 837 cases with cholelithiasis and 146 (3.5 %) of 4,173 controls had received bevacizumab in the 180 days before the index date. No significant association existed between cholelithiasis and exposure to bevacizumab (adjusted OR 0.82; 95 % CI 0.53–1.29;

Table 1 Baseline characteristics of cases and matched controls[a]

Characteristics	Upper GI ulceration			Diverticular disease		
	Cases ($n = 908$)	Controls ($n = 4,535$)	Standardized difference[b]	Cases ($n = 986$)	Controls ($n = 4,890$)	Standardized difference[b]
Demographics						
Mean (95 % CI) age at index date	79.5 (79.0–80.0)	79.5 (79.3–79.7)	0	79.2 (78.7–79.7)	79.1 (78.9–79.3)	0.01
Male gender	369 (40.6)	1,844 (40.7)	0	321 (32.6)	1,589 (32.5)	0
Income quintile[c]						
Missing	≤5 (0.6)	23 (0.5)	–	≤5 (0.1)	25 (0.5)	–
1	218 (24.0)	835 (18.4)	–	192 (19.5)	911 (18.6)	–
2	189 (20.8)	903 (19.9)	–	207 (21.0)	1,022 (20.9)	–
3	168 (18.5)	855 (18.9)	–	201 (20.4)	943 (19.3)	–
4	178 (19.6)	916 (20.2)	–	197 (20.0)	1,027 (21.0)	–
5	150 (16.5)	1,003 (22.1)	–	188 (19.1)	962 (19.7)	–
Comorbidities						
Mean (95 % CI) no. of unique drugs prescribed in previous year	15.7 (15.1–16.3)	11.1 (10.9–11.3)	0.6	15.3 (14.8–15.8)	11.3 (11.1–11.5)	0.54
Diabetes	361 (39.8)	1,511 (33.3)	0.14	330 (33.5)	1,596 (32.6)	0.02
Evidence of alcohol use disorder	15 (1.7)	20 (0.4)	0.15	≤5 (0.4)	18 (0.4)	0.01
Any cancer	103 (11.3)	376 (8.3)	0.11	102 (10.3)	384 (7.9)	0.09
Pancreatic cancer	≤5 (0.2)	≤5 (0.0)	0.08	0 (0.0)	≤5 (0.1)	0.03
Endoscopic retrograde cholangiopancreatography	≤5 (0.1)	≤5 (0.1)	0.02	≤5 (0.2)	≤5 (0.0)	0.08
Chronic kidney disease	96 (10.6)	132 (2.9)	0.39	65 (6.6)	129 (2.6)	0.22
Drugs used in previous year						
HRT	18 (2.0)	142 (3.1)	0.07	40 (4.1)	177 (3.6)	0.02
ACE inhibitors	392 (43.2)	1,699 (37.5)	0.12	399 (40.5)	1,815 (37.1)	0.07
Bisphosphonates	189 (20.8)	1,059 (23.4)	0.06	234 (23.7)	1,114 (22.8)	0.02
NSAIDs (excluding COX-2)	347 (38.2)	1,269 (28.0)	0.22	339 (34.4)	1,323 (27.1)	0.16
PPIs	600 (66.1)	1,518 (33.5)	0.69	488 (49.5)	1,622 (33.2)	0.34
Mesalamine	6 (0.7)	10 (0.2)	0.08	7 (0.7)	17 (0.3)	0.06
Valproic acid	≤5 (0.1)	11 (0.2)	0.03	≤5 (0.3)	25 (0.5)	0.03
Opiates	367 (40.4)	1,187 (26.2)	0.32	418 (42.4)	1,319 (27.0)	0.34
Glucocorticoids	132 (14.5)	384 (8.5)	0.21	158 (16.0)	455 (9.3)	0.22
Sulphonamides	80 (8.8)	223 (4.9)	0.17	101 (10.2)	241 (4.9)	0.23
Thiazide diuretics	319 (35.1)	1,329 (29.3)	0.13	305 (30.9)	1,477 (30.2)	0.02
Furosemide	239 (26.3)	696 (15.3)	0.29	208 (21.1)	790 (16.2)	0.13
Fibrates	28 (3.1)	82 (1.8)	0.09	38 (3.9)	93 (1.9)	0.13
H2 blocking anti-histamines	138 (15.2)	394 (8.7)	0.22	109 (11.1)	420 (8.6)	0.09
Progesterone	≤5 (0.2)	19 (0.4)	0.03	≤5 (0.4)	22 (0.4)	0.01
COX-2 inhibitors	58 (6.4)	215 (4.7)	0.08	67 (6.8)	250 (5.1)	0.07
History of outcome	30 (3.3)	145 (3.2)	0.01	100 (10.1)	460 (9.4)	0.03

Table 1 continued

Characteristics	Pancreatitis			Cholelithiasis		
	Cases ($n = 908$)	Controls ($n = 4,535$)	Standardized difference[b]	Cases ($n = 986$)	Controls ($n = 4,890$)	Standardized difference[b]
Demographics						
Mean (95 % CI) age at index date	79.5 (78.8–80.2)	79.5 (79.2–79.8)	0	79.3 (78.9–79.8)	79.3 (79.1–79.5)	0.01
Male gender	197 (39.4)	966 (39.1)	0.01	351 (41.9)	1,748 (41.9)	0
Income quintile[c]						
Missing	≤5 (0.2)	9 (0.4)	–	≤5 (0.5)	24 (0.6)	–
1	104 (20.8)	451 (18.3)	–	172 (20.5)	786 (18.8)	–
2	101 (20.2)	528 (21.4)	–	149 (17.8)	878 (21.0)	–
3	98 (19.6)	438 (17.7)	–	195 (23.3)	809 (19.4)	–
4	107 (21.4)	542 (22.0)	–	173 (20.7)	853 (20.4)	–
5	89 (17.8)	500 (20.3)	–	144 (17.2)	823 (19.7)	–
Comorbidities						
Mean (95 % CI) no. of unique drugs prescribed in previous year	14.0 (13.3–14.7)	11.3 (11.0–11.6)	0.36	14.3 (13.7–14.9)	11.0 (10.8–11.3)	0.43
Diabetes	198 (39.6)	836 (33.9)	0.12	307 (36.7)	1,370 (32.8)	0.08
Evidence of alcohol use disorder	≤5 (0.8)	≤5 (0.2)	0.11	8 (1.0)	11 (0.3)	0.11
Any cancer	55 (11.0)	221 (9.0)	0.07	93 (11.1)	322 (7.7)	0.12
Pancreatic cancer	≤5 (0.4)	0 (0.0)	0.15	≤5 (0.2)	≤5 (0.0)	0.09
Endoscopic retrograde cholangiopancreatography	17 (3.4)	≤5 (0.0)	0.44	57 (6.8)	0 (0.0)	0.66
Chronic kidney disease	43 (8.6)	67 (2.7)	0.31	47 (5.6)	98 (2.3)	0.2
Drugs used in previous year						
HRT	17 (3.4)	91 (3.7)	0.02	37 (4.4)	120 (2.9)	0.09
ACE inhibitors	217 (43.4)	939 (38.0)	0.11	372 (44.4)	1,566 (37.5)	0.14
Bisphosphonates	112 (22.4)	552 (22.4)	0	176 (21.0)	926 (22.2)	0.03
NSAIDs (excluding COX-2)	151 (30.2)	705 (28.6)	0.04	267 (31.9)	1,176 (28.2)	0.08
PPIs	258 (51.6)	829 (33.6)	0.38	437 (52.2)	1,345 (32.2)	0.42
Mesalamine	≤5 (0.4)	≤5 (0.1)	0.07	≤5 (0.1)	11 (0.3)	0.03
Valproic acid	≤5 (0.4)	8 (0.3)	0.01	≤5 (0.2)	10 (0.2)	0
Opiates	192 (38.4)	673 (27.3)	0.25	376 (44.9)	1,115 (26.7)	0.4
Glucocorticoids	58 (11.6)	237 (9.6)	0.07	120 (14.3)	339 (8.1)	0.22
Sulphonamides	43 (8.6)	124 (5.0)	0.16	48 (5.7)	215 (5.2)	0.03
Thiazide diuretics	162 (32.4)	730 (29.6)	0.06	287 (34.3)	1,205 (28.9)	0.12
Furosemide	128 (25.6)	402 (16.3)	0.24	188 (22.5)	666 (16.0)	0.17
Fibrates	26 (5.2)	54 (2.2)	0.19	28 (3.3)	98 (2.3)	0.06
H2 blocking anti-histamines	43 (8.6)	194 (7.9)	0.03	90 (10.8)	365 (8.7)	0.07
Progesterone	0 (0.0)	10 (0.4)	0.07	8 (1.0)	18 (0.4)	0.07
COX-2 inhibitors	25 (5.0)	118 (4.8)	0.01	38 (4.5)	186 (4.5)	0
History of outcome	35 (7.0)	143 (5.8)	0.05	37 (4.4)	173 (4.1)	0.01

Table 1 continued

Characteristics	Cholelithiasis		
	Cases ($n = 837$)	Controls ($n = 4,173$)	Standardized difference[b]
Demographics			
Mean (95 % CI) age at index date	79.6 (78.9–80.4)	79.6 (79.3–80.0)	0
Male gender	164 (46.7)	820 (46.8)	0
Income quintile[c]			
Missing	≤5 (0.9)	8 (0.5)	–
1	80 (22.8)	329 (18.8)	–
2	63 (17.9)	332 (18.9)	–
3	65 (18.5)	351 (20.0)	–
4	67 (19.1)	–	–
5	73 (20.8)	374 (21.3)	–
Comorbidities			
Mean (95 % CI) no. of unique drugs prescribed in previous year	14.5 (13.6–15.5)	11.0 (10.6–11.3)	0.47
Diabetes	75 (21.4)	≤5 (0.1)	1.25
Evidence of alcohol use disorder	≤5 (0.9)	≤5 (0.2)	0.11
Any cancer	38 (10.8)	148 (8.4)	0.08
Pancreatic cancer	≤5 (0.3)	≤5 (0.1)	0.07
Endoscopic retrograde cholangiopancreatography	≤5 (0.6)	≤5 (0.1)	0.1
Chronic kidney disease	21 (6.0)	53 (3.0)	0.16
Drugs used in previous year			
HRT	≤5 (1.4)	46 (2.6)	0.08
ACE inhibitors	153 (43.6)	669 (38.1)	0.11
Bisphosphonates	79 (22.5)	363 (20.7)	0.04
NSAIDs (excluding COX-2)	116 (33.0)	464 (26.5)	0.15
PPIs	196 (55.8)	558 (31.8)	0.51
Mesalamine	≤5 (0.3)	≤5 (0.2)	0.03
Valproic acid	0 (0.0)	≤5 (0.2)	0.05
Opiates	148 (42.2)	455 (25.9)	0.36
Glucocorticoids	52 (14.8)	126 (7.2)	0.28
Sulphonamides	19 (5.4)	74 (4.2)	0.06
Thiazide diuretics	114 (32.5)	504 (28.7)	0.08
Furosemide	86 (24.5)	278 (15.8)	0.23
Fibrates	7 (2.0)	30 (1.7)	0.02
H2 blocking anti-histamines	35 (10.0)	153 (8.7)	0.04
Progesterone	≤5 (0.9)	≤5 (0.2)	0.11
COX-2 inhibitors	19 (5.4)	82 (4.7)	0.03
History of outcome	≤5 (1.4)	24 (1.4)	0

ACE angiotensin-converting enzyme, *CI* confidence interval, *COX* cyclooxygenase, *GI* gastrointestinal, *HRT* hormone-replacement therapy, *NSAIDs* non-steroidal anti-inflammatory drugs, *PPI* protein pump inhibitor, *SD* standard deviation

[a] Values are n (percentages) unless stated otherwise. All cells with values of 5 or less are reported as ≤5 for privacy reasons. Up to five controls were matched to each case on age (±1 year), sex, and history of outcome

[b] Difference between cases and controls divided by pooled SD of two groups. Standardised differences <0.1 indicate good balance between groups [45]

[c] Income was estimated from neighbourhood income quintiles based on Statistics Canada census data

Outcome	Exposure	No (%) of Patients		Odds Ratio (95% CI)	
		Case	Control	Unadjusted [b]	Adjusted [c]
Upper Gastrointestinal Ulceration		(n=908)	(n=4535)		
	Ranibizumab	48 (5.3)	226 (5.0)	1.07 (0.77-1.48)	1.25 (0.88-1.77)
	Bevacizumab	31 (3.4)	161 (3.6)	0.96 (0.65-1.42)	1.05 (0.69-1.61)
Diverticular Disease		(n=986)	(n=4890)		
	Ranibizumab	62 (6.3)	278 (5.7)	1.12 (0.84-1.49)	1.12 (0.83-1.52)
	Bevacizumab	32 (3.2)	122 (2.5)	1.30 (0.87-1.95)	1.29 (0.86-1.96)
Pancreatitis		(n=500)	(n=2468)		
	Ranibizumab	26 (5.2)	124 (5.0)	1.04 (0.67-1.62)	0.85 (0.51-1.40)
	Bevacizumab	17 (3.4)	70 (2.8)	1.20 (0.70-2.06)	1.49 (0.84-2.63)
Cholelithiasis		(n=837)	(n=4173)		
	Ranibizumab	36 (4.3)	243 (5.8)	0.72 (0.50-1.03)	0.77 (0.53-1.11)
	Bevacizumab	24 (2.9)	146 (3.5)	0.81 (0.52-1.26)	0.82 (0.53-1.29)
Cholecystitis		(n=351)	(n=1754)		
	Ranibizumab	15 (4.3)	94 (5.4)	0.78 (0.44-1.38)	0.83 (0.44-1.56)
	Bevacizumab	9 (2.6)	42 (2.4)	1.07 (0.52-2.23)	1.45 (0.67-3.12)

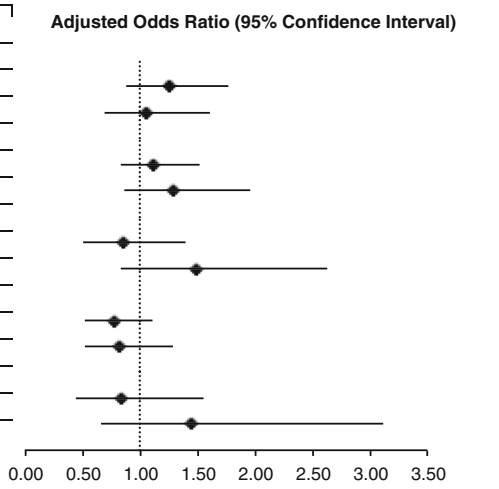

Fig. 1 Adverse events following intravitreal injections of vascular endothelial growth factor inhibitors. Reference group: non-use of either vascular endothelial growth factor inhibitor. [a] Matched on age, sex, and history of outcome. [b] Matched on age, sex, and history of outcome; adjusted for as follows: *1* upper GI ulceration: no. of unique drugs prescribed, CKD in previous 5 years, evidence of alcohol use disorder in previous 2 years, NSAIDs, COX-2 inhibitors, PPIs, H2 blocking anti-histamines, glucocorticoids; *2* diverticular disease: no. of unique drugs prescribed, CKD in previous 5 years, glucocorticoids; *3* pancreatitis: no. of unique drugs prescribed, CKD in previous 5 years, evidence of alcohol use disorder in previous 2 years, diabetes, cholelithiasis or cholecystitis in past year, endoscopic retrograde cholangiopancreatography in past 3 months, opiates, sulphonamides, ACE inhibitors, furosemide, fibrates; *4* cholelithiasis: no. of unique drugs prescribed, CKD in previous 5 years, diabetes, hormone-replacement therapy, fibrates, progesterone; *5* cholecystitis: no. of unique drugs prescribed, CKD in previous 5 years, diabetes, hormone-replacement therapy, fibrates, progesterone. *ACE* angiotensin-converting enzyme, *CKD* chronic kidney disease, *COX* cyclooxygenase, *GI* gastrointestinal, *NSAIDs* non-steroidal anti-inflammatory drugs, *PPI* protein pump inhibitor

Fig. 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with cholelithiasis (adjusted OR 1.13; 95 % CI 0.62–2.05; Fig. 2).

3.6 Association between Cholecystitis and VEGF Inhibitors

In our primary analysis, 15 (4.3 %) of 351 cases with cholecystitis and 94 (5.4 %) of 1,754 controls had received ranibizumab in the 180 days before the index date. We found no statistically significant association between cholecystitis and exposure to ranibizumab (adjusted OR 0.83; 95 % CI 0.44–1.56; Fig. 1). Nine (2.6 %) of 351 cases with cholecystitis and 42 (2.4 %) of 1,754 controls had received bevacizumab in the 180 days before the index date. No significant association existed between cholecystitis and exposure to bevacizumab (adjusted OR 1.45; 95 % CI 0.67–3.12; Fig. 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with cholecystitis (adjusted OR 1.95; 95 % CI 0.71–5.36; Fig. 2).

4 Discussion

Despite widespread use of intravitreal bevacizumab and ranibizumab, concerns have persisted regarding the risks of adverse GI and pancreaticobiliary events in this setting [4, 18, 24, 25]. Our population-based study suggests that intravitreal injections of bevacizumab and ranibizumab are not associated with increased risks of upper GI ulceration, diverticular disease, pancreatitis, cholelithiasis, and cholecystitis. Further, intravitreal injections of bevacizumab and ranibizumab do not appear to impart differing risks of adverse GI outcomes.

Previous studies have shown associations between the systemic use of bevacizumab as an intravenous treatment for cancer and GI adverse events [14–17]. Further, clinical trials of intravitreal bevacizumab and ranibizumab in AMD treatment have suggested higher risks of adverse outcomes with the use of bevacizumab driven by increased risks of adverse GI and pancreaticobiliary events [4, 18, 19]. However, because clinical trials are generally not designed or powered to adequately evaluate uncommon adverse events and may be poorly generalizable to the types of patients treated in clinical practice, large-scale post-marketing studies such as ours provide important information

Outcome	Exposure	No (%) of Patients		Odds Ratio (95% CI)	
		Case	Control	Unadjusted [a]	Adjusted [b]
Upper Gastrointestinal Ulceration		(n=908)	(n=4535)		
	Ranibizumab	43 (4.74)	200 (4.41)	1 [reference]	1 [reference]
	Bevacizumab	26 (2.86)	135 (2.98)	0.89 (0.52-1.54)	0.86 (0.48-1.54)
Diverticular Disease		(n=986)	(n=4890)		
	Ranibizumab	56 (5.68)	259 (5.30)	1 [reference]	1 [reference]
	Bevacizumab	26 (2.64)	103 (2.11)	1.17 (0.69-1.98)	1.17 (0.69-2.01)
Pancreatitis		(n=500)	(n=2468)		
	Ranibizumab	24 (4.80)	113 (4.58)	1 [reference]	1 [reference]
	Bevacizumab	15 (3.00)	59 (2.39)	1.19 (0.57-2.47)	1.79 (0.81-3.95)
Cholelithiasis		(n=837)	(n=4173)		
	Ranibizumab	35 (4.18)	215 (5.15)	1 [reference]	1 [reference]
	Bevacizumab	23 (2.75)	118 (2.83)	1.23 (0.68-2.22)	1.13 (0.62-2.05)
Cholecystitis		(n=351)	(n=1754)		
	Ranibizumab	15 (4.27)	85 (4.85)	1 [reference]	1 [reference]
	Bevacizumab	9 (2.56)	33 (1.88)	1.60 (0.62-4.10)	1.95 (0.71-5.36)

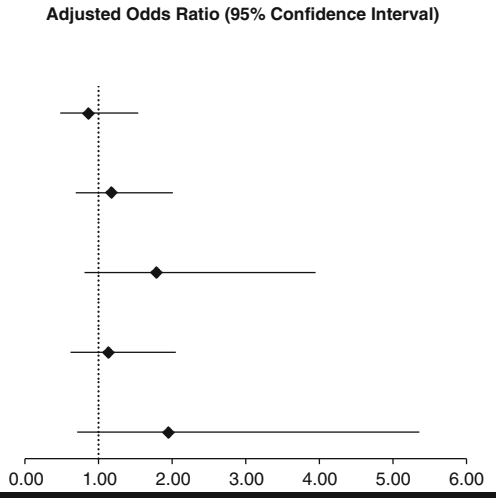

Fig. 2 Risk of adverse events among exclusive users of bevacizumab or ranibizumab. [a] Matched on age, sex, and history of outcome. [b] Matched on age, sex, and history of outcome; adjusted for as follows: *1* upper GI ulceration: no. of unique drugs prescribed, CKD in previous 5 years, evidence of alcohol use disorder in previous 2 years, NSAIDs, COX-2 inhibitors, PPIs, H2 blocking anti-histamines, glucocorticoids; *2* diverticular disease: no. of unique drugs prescribed, CKD in previous 5 years, glucocorticoids; *3* pancreatitis: no. of unique drugs prescribed, CKD in previous 5 years, evidence of alcohol use disorder in previous 2 years, diabetes, cholelithiasis or cholecystitis in past year, endoscopic retrograde cholangiopancreatography in past 3 months, opiates, sulphonamides, ACE inhibitors, furosemide, fibrates; *4* cholelithiasis: no. of unique drugs prescribed, CKD in previous 5 years, diabetes, hormone-replacement therapy, fibrates, progesterone; *5* cholecystitis: no. of unique drugs prescribed, CKD in previous 5 years, diabetes, hormone-replacement therapy, fibrates, progesterone. *ACE* angiotensin-converting enzyme, *CKD* chronic kidney disease, *COX* cyclooxygenase, *GI* gastrointestinal, *NSAIDs* non-steroidal anti-inflammatory drugs, *PPI* protein pump inhibitor

on safety that complements data from clinical trials [21, 22].

Strengths of our study include the large, population-based study cohort, which maximized generalizability and provided for complete matching of most cases. Further, we examined several important, biologically plausible outcomes involving both the upper and the lower GI tract as well as the pancreaticobiliary system and found consistent results. Adjustment for multiple confounders and the use of validated databases are further strengths of our study. Because we studied a population with a universal healthcare system and public insurance coverage of ranibizumab, we were able to avoid unmeasured confounding factors underlying the choice between drugs at the individual level, including socioeconomic status.

There are some limitations to our study that warrant mention. First, adverse events that did not lead to hospital admission or an emergency department visit were not captured. This likely had minimal effect on our findings, as most clinically important events are severe enough to result in emergency department visits or hospital admissions. Second, severe events leading to death outside of hospital were not captured. However, this would be expected to be rare for the outcomes we investigated and any instances would be expected to be non-differential. Third, the indirect ascertainment of bevacizumab exposure could cause misclassification of exposure to this drug. However, we used a series of strategies to reduce the risk of exposure misclassification, and sensitivity analyses showed our results to be robust. Fourth, to receive intravitreal injections, patients needed to be healthy enough to attend outpatient clinics. As a result, despite comorbidity adjustments, residual confounding could have made both VEGF inhibitors appear safer than they are in reality. However, this would not be expected to affect comparisons of risk between the two drugs. Fifth, alternative look-back periods were not evaluated. However, our study used a look-back period based on trials of bevacizumab as a cancer therapy, which showed that serious adverse events do not occur immediately after drug exposure. In particular, a meta-analysis found that the median time to stroke was 2.6 months in bevacizumab-treated cancer patients [11]. Hence, assuming an interquartile range of approximately half of the median, a look-back period of 180 days would be expected to capture most serious systemic events associated with VEGF inhibition. Finally, while we adjusted for a large number of covariates, including diabetes, residual confounding by the severity of diabetes and smoking could bias toward higher adverse event rates among those exposed to VEGF inhibitors. However, as we did not find

increased risks of exposure among cases, this appears unlikely to have influenced our conclusions. Further, this would not affect comparisons between drugs.

In conjunction with efficacy data from a number of clinical trials, including the Comparison of Age-related Macular Degeneration Treatments Trials and the Inhibit Vascular Endothelial Growth Factor in Age-related Choroidal Neovascularisation studies, our safety data support the use of bevacizumab in the treatment of ocular diseases [4, 19]. However, it is important to address risks associated with reconstitution in compounding pharmacies. The potential risks of compounding were highlighted by a recent outbreak of fungal meningitis resulting from improper techniques in the preparation of drugs given by epidural injection [46]. Hence, reliable and accountable processes must surround the use of bevacizumab as an intravitreal therapy.

5 Conclusions

Objective and on-going appraisal of evidence lays the foundation for healthcare that maximizes quality, access, and value. Our population-based study suggests that intravitreal injections of bevacizumab and ranibizumab are not associated with increased risks of adverse GI events, and that the two drugs do not impart differing risks of adverse GI outcomes. Our findings complement results from clinical trials and will help to inform clinical decision making and drug policy regarding the adverse event profile and comparative safety of intravitreal VEGF inhibitors.

Contributors All authors were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. RJC drafted the manuscript and approved the final version to be published. SSG, SEB, JMP, MW, EdeLPC, and CMB critically revised the manuscript for important intellectual content. RJC, MW, SEB, SSG, and CMB conducted the statistical analysis. RJC and SSG obtained funding. RJC supervised the study and is the guarantor.

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Data Access and Responsibility Dr. RJ Campbell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest RJ Campbell, CM Bell, SE Bronskill, JM Paterson, M Whitehead, EdeL Campbell, and SS Gill have no conflicts of interest.

Role of the Sponsors The sponsors of this study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit for publication. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Ethical Approval The study protocol was approved by the Research Ethics Board at Queen's University, Kingston, Ontario, Canada (file No. 6004374).

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