

RESEARCH

Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study

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Abstract

Objective To assess the risk of systemic adverse events associated with intravitreal injections of vascular endothelial growth factor inhibiting drugs.

Design Population based nested case-control study.

Setting Ontario, Canada.

Participants 91 378 older adults with a history of physician diagnosed retinal disease identified between 1 April 2006 and 31 March 2011. Cases were 1477 patients admitted to hospital for ischaemic stroke, 2229 admitted for an acute myocardial infarction, 1059 admitted or assessed in an emergency department for venous thromboembolism, and 2623 admitted for congestive heart failure. Event-free controls (at a ratio of 5:1) were matched to cases on the basis of year of birth, sex, history of the outcome in the previous 5 years, and diabetes.

Main exposure measure Exposure to vascular endothelial growth factor inhibiting drugs identified within 180 days before the index date.

Results After adjustment for potential confounders, participants who had ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism were not more likely than control participants to have been exposed to either bevacizumab (adjusted odds ratios of 0.95 (95% confidence interval 0.68 to 1.34) for ischaemic stroke, 1.04 (0.77 to 1.39) for acute myocardial infarction, 0.81 (0.49 to 1.34) for venous thromboembolism, and 1.21 (0.91 to 1.62) for congestive heart failure) or ranibizumab (adjusted odds ratios 0.87 (0.68 to 1.10) for ischaemic stroke, 0.90 (0.72 to 1.11) for acute myocardial infarction, 0.88 (0.67 to 1.16) for venous thromboembolism, and 0.87 (0.70 to 1.07) for congestive heart failure). Similarly, a secondary analysis of exclusive

users of bevacizumab or ranibizumab showed no differences in risk between the two drugs (adjusted odds ratios for bevacizumab relative to ranibizumab of 1.03 (0.67 to 1.60) for ischaemic stroke, 1.23 (0.85 to 1.77) for acute myocardial infarction, 0.92 (0.51 to 1.69) for venous thromboembolism, and 1.35 (0.93 to 1.95) for congestive heart failure). These findings were consistent for all but one outcome in subgroup analyses.

Conclusions Intravitreal injections of bevacizumab and ranibizumab were not associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism.

Introduction

Age related macular degeneration is the leading cause of blindness in Western nations; the neovascular ("wet") subtype is responsible for most cases of severe vision loss.¹⁻⁴ Because vascular endothelial growth factor plays an important role in the growth of the pathological blood vessels that underlie neovascular age related macular degeneration, the development of vascular endothelial growth factor inhibitors has revolutionised the treatment of this disease.⁵⁻⁸ However, vascular endothelial growth factor functions in many physiological and pathological processes, including maintenance of normal blood vessels, wound healing responses, blood clotting processes, and stabilisation of atheromatous plaques.⁹⁻¹² These wide ranging effects make the hypothesis that adverse vascular events may stem from inhibition of vascular endothelial growth factor biologically plausible. Furthermore, empirical clinical evidence

suggests an association between inhibition of vascular endothelial growth factor and adverse vascular events. In particular, intravenous administration of the vascular endothelial growth factor inhibitor bevacizumab has been associated with increased risks of stroke, venous thromboembolism, and congestive heart failure.¹³⁻¹⁵ Whether this risk of systemic adverse events can be extrapolated to the small doses used in age related macular degeneration remains unclear.

Direct injection of vascular endothelial growth factor inhibitors into the eye decreases the concentration of drug reaching the systemic circulation.¹⁶⁻¹⁸ Clinical trials comparing intravitreal ranibizumab and bevacizumab with sham treated controls did not detect increased risks of vascular adverse events with either drug.^{6 7 19} In contrast, a small meta-analysis of early trials with ranibizumab found an increased risk of stroke in patients receiving ranibizumab injections.²⁰ The Comparison of Age-related Macular Degeneration Treatments Trials, which directly compared intravitreal bevacizumab against intravitreal ranibizumab, found a higher risk of adverse events among participants receiving bevacizumab.^{8 21} However, this finding is difficult to interpret given that most of the observed adverse events were conditions not previously associated with inhibition of vascular endothelial growth factor, and that participants who received fewer doses of bevacizumab had a greater risk than did those who received more.

Clinical trials and meta-analyses have several important limitations, including a lack of power to detect adverse events and often poor generalisability.²² Hence, large post-marketing studies provide important information on safety that complements data from clinical trials.²³ One previous population based study was inconclusive on the relative safety of ranibizumab and bevacizumab.²⁴ Although the study's primary analysis found that bevacizumab was associated with greater risk of stroke than was ranibizumab, the price gap between the drugs may have resulted in confounding due to differences in socioeconomic status between people receiving the two drugs. A secondary analysis from the same study, which controlled for the effect of socioeconomic status, found no difference in safety between the two drugs. Because of this discrepancy, questions regarding the risks of adverse events with intravitreal injection of vascular endothelial growth factor inhibiting drugs persist. To evaluate these risks, we did a population based, nested case-control study in a setting with universal healthcare insurance, which diminished the confounding effects of socioeconomic status.

Methods

Overview

We did a population based, nested case-control study to investigate the risk of serious adverse events associated with intravitreal injections of vascular endothelial growth factor inhibitors. We used linked healthcare databases to examine associations between four distinct outcomes (ischaemic stroke, acute myocardial infarction, venous thromboembolism, and congestive heart failure) and previous exposure to intravitreal injections of bevacizumab and ranibizumab.

Data sources

The province of Ontario provides universal healthcare insurance that covers all 13 million residents, and the resulting administrative data are population based. For this study, we linked records from seven health administrative databases. The Ontario Health Insurance Plan database contains information on inpatient and outpatient physician services and has excellent

reliability for recording of medical procedures.²⁵ The Ontario Drug Benefit database contains records of all outpatient prescriptions for formulary drugs dispensed to patients aged 65 years or older and has an error rate of less than 1%.^{25 26} The Canadian Institute for Health Information discharge abstract database provides detailed information on all hospital admissions in Ontario.²⁷ The National Ambulatory Care Reporting System database contains information on all visits to hospital emergency departments.^{28 29} The registered persons database contains demographic information on all residents, and the Ontario diabetes database contains validated information on Ontarians with diabetes.³⁰ The Institute for Clinical Evaluative Sciences physician database contains data on the specialty of all healthcare providers in Ontario. The databases used provide accurate data on the variables assessed in this study.²⁵⁻²⁷

Study population and base cohort identification

We used the Ontario Health Insurance Plan database to identify a base cohort consisting of patients diagnosed as having retinal disease (ICD-9 (international classification of diseases, 9th revision) code 362) within the previous two years who were aged 66 years and older between 1 April 2006 and 31 March 2011. We chose this period to include periods of significant use of both bevacizumab and ranibizumab in Ontario.³¹ To ensure that patients in the cohort could access intravitreal injections if clinically indicated, we limited our analysis to those who, during the study period, had seen an ophthalmologist who offered intravitreal injections.³¹

Study outcomes and case ascertainment

Cases were patients who were admitted to hospital with a primary diagnosis of ischaemic stroke (ICD-10 code I63 or I64), acute myocardial infarction (ICD-10 code I21), venous thromboembolism (ICD-10 code I26 or I80), or congestive heart failure (ICD-10 code I50). We defined the date of hospital admission or emergency department visit as the index date. Compared with direct chart review, the positive predictive values for the diagnoses of stroke and acute myocardial infarction in this database are both 87%.²⁷ Similarly, the coding for congestive heart failure was highly predictive of the diagnosis made using clinical criteria in another validation study.³² Because some cases of venous thromboembolism are managed without hospital admission, we also included patients who visited an emergency room with a primary diagnosis of venous thromboembolism (ICD-10 code I26 or I80). For each outcome, if patients had multiple occurrences we included only the first in our analysis. Patients who experienced one outcome remained eligible to be controls for cases who experienced one of the other outcomes. Patients selected as controls remained eligible to have outcome events subsequently.

Selection of controls

For each outcome, we selected up to five randomly selected controls for each case from the study population who had not experienced the adverse event. We assigned controls the same index date as their respective cases and matched them to cases according to year of birth, sex, history of the outcome in the five years preceding the index date, and diabetes.

Assessment of exposure to vascular endothelial growth factor inhibitors

We identified intravitreal injections of ranibizumab by using the Ontario Health Insurance Plan and Ontario Drug Benefit

databases.³¹ Ranibizumab has been covered by the Ontario Drug Benefit Program since 25 March 2008. Before that date, use of ranibizumab in Ontario was minimal.³¹ Bevacizumab does not have approval from Health Canada for use in age related macular degeneration and is not covered by the Ontario Drug Benefit Program for this indication. However, bevacizumab received Health Canada approval for use in colorectal cancer in September 2005, and physicians can bill the provincial physician insurance plan for off-label intravitreal injections of this drug. Our previous work has documented the widespread use of off-label bevacizumab in the period before coverage of ranibizumab by the public drug insurance plan.³¹

We assigned exposure to bevacizumab injection indirectly. We identified all intravitreal injection procedures that were not associated with a prescription for ranibizumab by using the Ontario Drug Benefit and Ontario Health Insurance Plan databases and used several strategies to reduce misclassification of intravitreal injections of gas, antibiotics, or steroids. Firstly, because gas is injected as part of retinal detachment therapy, we excluded injections given to patients with a proximate diagnosis of retinal detachment, defined as having had a vitreous exchange procedure or a retinal reattachment procedure within 42 days before or seven days after the intravitreal injection. Secondly, because intravitreal steroid is used for retinal conditions that are also treated with laser, we excluded injections given to patients who had had retinal laser treatment in the previous 180 days. Additionally, we did a sensitivity analysis in which this time frame was shortened to 42 days. Finally, because antibiotics are injected for postoperative endophthalmitis, we excluded injections given to patients who had had retinal surgery, cataract surgery, corneal surgery, or glaucoma surgery in the 42 days before the injection.

Covariates

We adjusted for several potential confounders. We used the number of distinct drugs dispensed in the year before the index date as a measure of comorbidity.^{33 34} We estimated income from neighbourhood fifths of income based on census data. We defined diabetes status on the basis of the validated Ontario diabetes database.³⁰ We identified patients with hypertension by using a validated algorithm.³⁵ We also adjusted for exposure to several specific drugs within the year before the index date, grouped by mechanism of action to avoid over-fitting the statistical models. We also included specific comorbidities (including atrial fibrillation, cancer, and renal failure) in the models.

Statistical analysis

We used descriptive statistics to characterise cases and controls. We used a nested case-control analysis to evaluate the association between exposure to intravitreal vascular endothelial growth factor inhibitor and each outcome.^{36 37} This approach provides unbiased estimates of the rate ratios that would be obtained from traditional time to event analyses of the full cohort, with little or no loss of precision.³⁸⁻⁴⁰

We used conditional logistic regression to estimate the odds ratios and 95% confidence intervals for the association between adverse outcomes and exposure to vascular endothelial growth factor inhibitor injections, controlling for potential confounding variables. In the primary analysis, we assessed the risk associated with exposure to bevacizumab or ranibizumab within 180 days before the adverse event. In a secondary analysis, to facilitate direct comparison between the two vascular endothelial growth factor inhibitors, we assessed the risk associated with

exclusive bevacizumab exposure (no ranibizumab exposure) by using exclusive ranibizumab exposure (no bevacizumab exposure) as the reference. Finally, we also did subgroup analyses on patients with and without diabetes.

For our study's case-control ratio of one to five, independence in the probability of exposure among cases and controls, and a type 1 error probability of 5%, our a priori estimates of power were 89% for ischaemic stroke, 99% for acute myocardial infarction, 71% for venous thromboembolism, and 99% for congestive heart failure to detect a clinically important unadjusted odds ratio of 1.5. This was based on conservative estimates including a base cohort of approximately 50 000 patients over the age of 65 with retinal disease in each of the five study years, with 5% exposure rates, and expected annual percentages experiencing adverse events of 0.5 for ischaemic stroke, 1.0 for acute myocardial infarction, 0.3 for venous thromboembolism, and 1.0 for congestive heart failure.^{31 41-43} All analyses were done at the Institute for Clinical Evaluative Sciences using SAS, version 9.2.

Results

Baseline characteristics of cases and controls

We identified 91 378 older people with retinal disease diagnosed by a physician over the five year study period. Within this base cohort, we identified 7388 cases, including 1477 (1.6%) cases of ischaemic stroke, 2229 (2.4%) of acute myocardial infarction, 1059 (1.2%) of venous thromboembolism, and 2623 (2.9%) of congestive heart failure. These were matched to 35 962 control patients, with 95% of cases matched to five controls. Tables 1, 2, 3, and 4 show the characteristics of cases and controls for the four outcomes. The percentage of patients with diabetes ranged from approximately 31% (venous thromboembolism; table 3) to approximately 53% (congestive heart failure; table 4). Case patients were slightly more likely than controls to come from the lowest fifth of population income. Comorbidities, including a history of cancer, chronic renal insufficiency, and atrial fibrillation, were more common among patients who experienced adverse outcomes. Similarly, case patients were prescribed more drugs than were controls in the year before the index date.

Association between ischaemic stroke and vascular endothelial growth factor inhibitors

In our primary analysis of 1477 case patients and 7349 control patients, 94 (6.4%) case patients had received ranibizumab in the 180 days before their stroke (index date), and 555 (7.6%) control subjects had received ranibizumab in the 180 days before the index date. We found no statistically significant association between stroke and exposure to ranibizumab (adjusted odds ratio 0.87, 95% confidence interval 0.68 to 1.10) (fig 1). Forty-four (3.0%) case patients had received bevacizumab in the 180 days before their stroke, and 238 (3.2%) control patients had received bevacizumab in the 180 days before the index date. No significant association existed between stroke and exposure to bevacizumab (adjusted odds ratio 0.95, 0.68 to 1.34) (fig 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with stroke (adjusted odds ratio 1.03, 0.67 to 1.60) (fig 2).

Association between acute myocardial infarction and vascular endothelial growth factor inhibitors

In our primary analysis of 2229 case patients and 11 010 control patients, 141 (6.3%) case patients had received ranibizumab in the 180 days before their acute myocardial infarction, and 797 (7.2%) control subjects had received ranibizumab in the 180 days before the index date. No significant association existed between acute myocardial infarction and exposure to ranibizumab (adjusted odds ratio 0.90, 0.72 to 1.11) (fig 1). Seventy-three (3.3%) case patients had received bevacizumab in the 180 days before their acute myocardial infarction, and 364 (3.3%) control patients had received bevacizumab in the 180 days before the index date. We found no significant association between acute myocardial infarction and exposure to bevacizumab (adjusted odds ratio 1.04, 0.77 to 1.39) (fig 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with acute myocardial infarction (adjusted odds ratio 1.23, 0.85 to 1.77) (fig 2).

Association between venous thromboembolism and vascular endothelial growth factor inhibitors

In our primary analysis of 1059 case patients and 5259 control patients, 74 (7.0%) case patients had received ranibizumab in the 180 days before their venous thromboembolism, and 425 (8.1%) controls had received ranibizumab in the 180 days before the index date. No significant association existed between venous thromboembolism and exposure to ranibizumab (adjusted odds ratio 0.88, 0.67 to 1.16) (fig 1). Twenty-one (2.0%) case patients had received bevacizumab in the 180 days before their venous thromboembolism, and 137 (2.6%) control patients had received bevacizumab in the 180 days before the index date. No significant association existed between venous thromboembolism and exposure to bevacizumab (adjusted odds ratio 0.81, 0.49 to 1.34) (fig 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with venous thromboembolism (adjusted odds ratio 0.92, 0.51 to 1.69) (fig 2).

Association between congestive heart failure and vascular endothelial growth factor inhibitors

In our primary analysis of 2623 case patients and 12 344 control patients, 166 (6.3%) case patients had received ranibizumab in the 180 days before being admitted for congestive heart failure, and 936 (7.6%) control patients had received ranibizumab in the 180 days before the index date. No significant association existed between congestive heart failure and exposure to ranibizumab (adjusted odds ratio 0.87, 0.70 to 1.07) (fig 1). Ninety-four (3.6%) case patients had received bevacizumab in the 180 days before being admitted for congestive heart failure, and 387 (3.1%) control patients had received bevacizumab in the 180 days before the index date. No significant association existed between congestive heart failure and exposure to bevacizumab (adjusted odds ratio 1.21, 0.91 to 1.62) (fig 1). In our secondary analysis, using exclusive ranibizumab exposure as the reference group, exclusive bevacizumab exposure was not significantly associated with congestive heart failure (adjusted odds ratio 1.35, 0.93 to 1.95) (fig 2).

Diabetes subgroup analyses

Our subgroup analyses of patients with and without diabetes showed no significant associations between either of the vascular endothelial growth factor inhibitors and any of the outcomes when compared with non-users (figure 3 and 4). Similarly, among both patients with and without diabetes, the secondary analysis of exclusive users showed no differences between bevacizumab and ranibizumab in the risk of ischaemic stroke, venous thromboembolism, or congestive heart failure (figures 5 and 6). In the subgroup with diabetes, we found a statistically significant association between exclusive bevacizumab exposure and acute myocardial infarction when exclusive ranibizumab exposure was used as the referent (adjusted odds ratio 1.76, 1.03 to 3.00) (fig 6).

Discussion

The results of our population based study suggest that, overall, intravitreal injections of bevacizumab and ranibizumab are not associated with increased risks of ischaemic stroke, acute myocardial infarction, venous thromboembolism, or congestive heart failure. Furthermore, our analyses suggest that the risks of ischaemic stroke, venous thromboembolism, and congestive heart failure do not differ significantly between bevacizumab and ranibizumab injections. Although we found a statistically significant association between acute myocardial infarction and exclusive bevacizumab use when compared with exclusive ranibizumab exposure in the subgroup with diabetes, our primary analysis and other secondary analyses did not detect any excess risk with either bevacizumab or ranibizumab. As a result, the finding in the diabetes subgroup should be interpreted cautiously given that multiple comparisons were made, raising the risk of a type 1 error, and the fact that this observation was limited to a single analysis of one outcome in one subgroup.

Comparison with other studies

Data from the pivotal clinical trials of bevacizumab and ranibizumab for age related macular degeneration have been inconclusive on the question of safety. Trials comparing intravitreal ranibizumab and bevacizumab against sham injection controls did not detect increased risks of vascular adverse events with either drug.^{6 7 19} However, a small meta-analysis of early trials with ranibizumab suggested an increased risk of stroke in patients receiving ranibizumab injections.²⁰ Additionally, direct comparison of intravitreal bevacizumab against intravitreal ranibizumab in the Comparison of Age-related Macular Degeneration Treatments Trials found a higher risk of adverse events among those receiving bevacizumab.^{8 21} However, most of the observed adverse events were conditions not previously associated with vascular endothelial growth factor inhibition.

Clinical trials and small meta-analyses have limitations including a lack of power to detect adverse events and poor generalisability to the types of patients who receive treatment in routine clinical practice.²² Hence, large scale post-marketing studies such as the one we present here provide important information on safety that complements data from clinical trials.²³ Overall, our results are consistent with conclusions of previous large observational studies on this topic, providing some reassurance that the widespread use of intravitreal injections of vascular endothelial growth factor inhibitors has not resulted in any clinically important increase in risk for individual patients.^{24 44} Although the primary analysis of a study of US Medicare patients suggested the possibility that bevacizumab is associated with a greater risk of stroke than is ranibizumab, a secondary analysis, which controlled for the confounding effects of socioeconomic

status and the price gap between ranibizumab and bevacizumab, did not confirm this difference in safety.^{24 45 46} Because of Ontario's universal coverage of ranibizumab for people over the age of 65, we were able to reduce the potential confounding effects of socioeconomic status in our study. An unpublished study of Medicare patients has suggested an increased risk of death and haemorrhagic stroke with bevacizumab when compared with ranibizumab.⁴⁷ Publication of these results as well as details regarding how the confounding effects of socioeconomic status were handled will add to our understanding.

Strengths and limitations of study

Strengths of our study include the large, real world study cohort and the population based approach, which maximised generalisability. The large population studied also provided for complete matching of most cases. We examined several important, biologically plausible outcomes and found largely consistent results. The use of validated databases and matching on important potential confounders are further strengths of our study. Our study also benefitted from the rapid transition from use of bevacizumab to ranibizumab in Ontario, which was induced by a shift in the coverage policy of the public drug plan.³¹ This allowed us to avoid the often unmeasured confounding factors underlying choices between drugs at the individual level, including socioeconomic status.

Several limitations to our study also warrant highlighting. Firstly, we did not capture adverse events that did not lead to hospital admission or an emergency department visit. This probably had a minimal effect on our findings, as the outcomes examined are generally severe enough to result in emergency department visits or hospital admissions. Secondly, we also did not capture severe events leading to death outside of hospital. Thirdly, because bevacizumab is used as an off-label treatment for age related macular degeneration, the indirect ascertainment of 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. Fourthly, to receive intravitreal injections, patients must be healthy enough to attend outpatient clinics. As a result, despite our adjustments for comorbidity, residual confounding could have made both bevacizumab and ranibizumab appear safer than they are in reality when compared with non-use (that is, no intravitreal injections). However, this would not be expected to affect comparisons of risk between the two drugs. Finally, although our estimates generally showed no increased or decreased risk with the use of intravitreal bevacizumab and ranibizumab, the observed confidence intervals include some potentially clinically relevant differences in risk, especially in the subgroup analyses.

Conclusions and policy implications

Because of the enormous costs involved, policies on the use of intravitreal vascular endothelial growth factor inhibitors have broad implications for healthcare systems.⁴⁸ For instance, despite considerable use of bevacizumab, ranibizumab sales in the United States surpassed \$1.6bn (£1.0bn; €1.3bn) in 2011, making ranibizumab the single greatest drug expenditure covered under Medicare part B.^{49 50} Bevacizumab costs approximately \$50-70 per injection, and ranibizumab is priced at about \$2000 per injection,⁸ and public leaders in the United States have recently requested a national coverage determination supporting the use of bevacizumab for age related macular degeneration.⁵¹ Similarly, the UK Department of Health, through the National Institute for Health and Clinical Excellence, has

begun working towards formally evaluating bevacizumab for age related macular degeneration, and corresponding evaluations are anticipated in many other countries.^{52 53}

Our results suggest that, overall, intravitreal injections of bevacizumab and ranibizumab are not associated with significant risks of ischaemic stroke, acute myocardial infarction, venous thromboembolism, or congestive heart failure. In conjunction with data from efficacy 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 age related macular degeneration.^{8 54} However, several important questions require clarification. In particular, further studies focusing on the risk of acute myocardial infarction in patients with diabetes treated with intravitreal vascular endothelial growth factor inhibitors are warranted. Additionally, the potential for bevacizumab's low price to discourage investment in innovative treatments for age related macular degeneration, and the need to design safe and accountable processes to support distribution of bevacizumab for intravitreal use, remain important.⁵⁵⁻⁵⁷ Furthermore, the entrance of additional vascular endothelial growth factor inhibitors onto the market will necessitate further comparative studies of effectiveness and safety. Clearly, with billions of dollars of healthcare at stake, stakeholders on all sides—from patients and physicians to governments, third party payers, and industry—must continue to evaluate all available data to ensure that accessibility, affordability, and quality of care are maximised.

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Contributors: All authors were involved in the study concept and design and in the analysis and interpretation of data. RJC drafted the manuscript and approved the final version to be published. SSG, SEB, JMP, MW, and CMB critically revised the manuscript for important intellectual content. RJC, MW, SEB, SSG, and CMB did the statistical analysis. RJC and SSG obtained funding. RJC, SEB, and SSG supervised the study. RJC is the guarantor.

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What is already known on this topic

Intravenous administration of vascular endothelial growth factor inhibitors for cancer has been associated with several adverse vascular events

Clinical trials have been inconclusive regarding the risks associated with the smaller doses of vascular endothelial growth factor inhibitors used to treat age related macular degeneration

What this study adds

This population based, nested case-control study was carried out in a setting with universal healthcare insurance to minimise the confounding effects of socioeconomic status

Overall, intravitreal injections of neither bevacizumab nor ranibizumab were associated with increased risks of ischaemic stroke, acute myocardial infarction, venous thromboembolism, or congestive heart failure

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

Data sharing: No additional data available.

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Tables

Table 1 | Baseline characteristics of cases of ischaemic stroke and matched controls*. Values are numbers (percentages) unless stated otherwise

Characteristics	Cases (n=1477)	Controls (n=7349)	Standardised difference†
Demographics			
Mean (95% CI) age at index date	81.8 (81.4 to 82.2)	81.8 (81.7 to 82.0)	0
Male sex	591 (40.0)	2946 (40.1)	0
Fifth of income:			
Missing	≤5 (0.1)	31 (0.4)	0.05
1	314 (21.3)	1420 (19.3)	0.05
2	341 (23.1)	1530 (20.8)	0.05
3	297 (20.1)	1516 (20.6)	0.01
4	276 (18.7)	1418 (19.3)	0.01
5	247 (16.7)	1434 (19.5)	0.01
Rural residence	238 (16.1)	1027 (14.0)	0.06
Comorbidities			
Mean (SD) No of unique drugs prescribed in previous year	14.2 (8.1)	12.2 (7.5)	0.25
Atrial fibrillation	674 (45.6)	1986 (27.0)	0.41
Coronary artery bypass grafting surgery	37 (2.5)	143 (1.9)	0.04
Cancer	120 (8.1)	414 (5.6)	0.1
Chronic renal insufficiency	129 (8.7)	283 (3.9)	0.23
Diabetes	633 (42.9)	3141 (42.7)	0
Drugs used in previous year			
Angiotensin converting enzyme inhibitors	712 (48.2)	2911 (39.6)	0.18
Angiotensin receptor blockers	386 (26.1)	1731 (23.6)	0.06
Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins)	825 (55.9)	3645 (49.6)	0.13
Clopidogrel	212 (14.4)	541 (7.4)	0.25
Warfarin	346 (23.4)	962 (13.1)	0.29
Acetylsalicylic acid/dipyridamole	118 (8.0)	157 (2.1)	0.34
Hormone replacement therapy	19 (1.3)	71 (1.0)	0.03
Low molecular weight heparin	24 (1.6)	69 (0.9)	0.07
Diuretics	781 (52.9)	3383 (46.0)	0.14
Diuretics, potassium sparing	116 (7.9)	509 (6.9)	0.04
Calcium channel blocker	652 (44.1)	2825 (38.4)	0.12
History of outcome			
Ischaemic stroke	64 (4.3)	284 (3.9)	0.02

All cells with values of 5 or less are reported as ≤5 for privacy reasons.

*Up to 5 controls were matched to each case on age (±1 year), sex, diabetes, and history of outcome.

†Difference between cases and controls divided by pooled standard deviation of two groups; standardised differences <0.1 indicate good balance between groups.

Table 2| Baseline characteristics of cases of acute myocardial infarction and matched controls*. Values are numbers (percentages) unless stated otherwise

Characteristics	Cases (n=2229)	Controls (n=11 010)	Standardised difference†
Demographics			
Mean (95% CI) age at index date	80.6 (80.3 to 80.9)	80.5 (80.4 to 80.7)	0.01
Male sex	1129 (50.7)	5578 (50.7)	0
Fifth of income:			
Missing	13 (0.6)	49 (0.4)	0.03
1	505 (22.7)	2066 (18.8)	0.1
2	445 (20.0)	2282 (20.7)	0.01
3	443 (19.9)	2181 (19.8)	0
4	442 (19.8)	2241 (20.4)	0.02
5	381 (17.1)	2191 (19.9)	0.07
Rural residence	401 (18.0)	1584 (14.4)	0.1
Comorbidities			
Mean (SD) No of unique drugs prescribed in previous year	17.1 (8.5)	12.1 (7.3)	0.64
Atrial fibrillation	740 (33.2)	2021 (18.4)	0.37
Coronary artery bypass grafting surgery	61 (2.7)	314 (2.9)	0.01
Cancer	183 (8.2)	613 (5.6)	0.11
Chronic renal insufficiency	340 (15.3)	418 (3.8)	0.5
Diabetes	1098 (49.3)	5374 (48.8)	0.01
Drugs used in previous year			
Angiotensin converting enzyme inhibitors	1284 (57.6)	4571 (41.5)	0.33
Angiotensin receptor blockers	616 (27.6)	2584 (23.5)	0.1
Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins)	1616 (72.5)	5860 (53.2)	0.39
Clopidogrel	832 (37.3)	786 (7.1)	0.98
Warfarin	397 (17.8)	1403 (12.7)	0.15
Acetylsalicylic acid/dipyridamole	52 (2.3)	222 (2.0)	0.02
Hormone replacement therapy	16 (0.7)	82 (0.7)	0
Low molecular weight heparin	28 (1.3)	114 (1.0)	0.02
Diuretics	1347 (60.4)	5106 (46.4)	0.28
Diuretics, potassium sparing	230 (10.3)	784 (7.1)	0.12
Calcium channel blocker	1090 (48.9)	4104 (37.3)	0.24
History of outcome			
Acute myocardial infarction	181 (8.1)	773 (7.0)	0.04

All cells with values of 5 or less are reported as ≤5 for privacy reasons.

*Up to 5 controls were matched to each case on age (± 1 year), sex, diabetes, and history of outcome.

†Difference between cases and controls divided by pooled standard deviation of two groups; standardised differences <0.1 indicate good balance between groups.

Table 3| Baseline characteristics of cases of venous thromboembolism and matched controls*. Values are numbers (percentages) unless stated otherwise

Characteristics	Cases (n=1059)	Controls (n=5259)	Standardised difference†
Demographics			
Mean (95% CI) age at index date	79.0 (78.5 to 79.4)	79.0 (78.8 to 79.2)	0
Male sex	402 (38.0)	1987 (37.8)	0
Fifth of income:			
Missing	≤5 (0.4)	23 (0.4)	0
1	214 (20.2)	991 (18.8)	0.04
2	231 (21.8)	1032 (19.6)	0.05
3	213 (20.1)	999 (19.0)	0.03
4	203 (19.2)	1122 (21.3)	0.05
5	194 (18.3)	1092 (20.8)	0.06
Rural residence	173 (16.3)	759 (14.4)	0.05
Comorbidities			
Mean (SD) No of unique drugs prescribed in previous year	15.0 (8.1)	11.3 (7.2)	0.49
Atrial fibrillation	272 (25.7)	905 (17.2)	0.22
Coronary artery bypass grafting surgery	20 (1.9)	95 (1.8)	0.01
Cancer	145 (13.7)	278 (5.3)	0.34
Chronic renal insufficiency	61 (5.8)	135 (2.6)	0.18
Diabetes	327 (30.9)	1618 (30.8)	0
Drugs used in previous year			
Angiotensin converting enzyme inhibitors	408 (38.5)	1992 (37.9)	0.01
Angiotensin receptor blockers	248 (23.4)	1178 (22.4)	0.02
Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins)	499 (47.1)	2524 (48.0)	0.02
Clopidogrel	82 (7.7)	301 (5.7)	0.08
Warfarin	305 (28.8)	582 (11.1)	0.52
Acetylsalicylic acid/dipyridamole	20 (1.9)	94 (1.8)	0.01
Hormone replacement therapy	14 (1.3)	48 (0.9)	0.04
Low molecular weight heparin	128 (12.1)	51 (1.0)	0.69
Diuretics	551 (52.0)	2242 (42.6)	0.19
Diuretics, potassium sparing	100 (9.4)	325 (6.2)	0.13
Calcium channel blocker	399 (37.7)	1768 (33.6)	0.09
History of outcome			
Venous thromboembolism	46 (4.3)	194 (3.7)	0.03

All cells with values of 5 or less are reported as ≤5 for privacy reasons.

*Up to 5 controls were matched to each case on age (± 1 year), sex, diabetes, and history of outcome.

†Difference between cases and controls divided by pooled standard deviation of two groups; standardised differences <0.1 indicate good balance between groups.

Table 4| Baseline characteristics of cases of congestive heart failure and matched controls*. Values are numbers (percentages) unless stated otherwise

Characteristics	Cases (n=2623)	Controls (n=12 344)	Standardised difference†
Demographics			
Mean (95% CI) age at index date	82.0 (81.7 to 82.3)	82.0 (81.9 to 82.2)	0
Male sex	1196 (45.6)	5636 (45.7)	0
Fifth of income:			
Missing	12 (0.5)	42 (0.3)	0.03
1	552 (21.0)	2425 (19.6)	0.04
2	569 (21.7)	2566 (20.8)	0.02
3	553 (21.1)	2484 (20.1)	0.02
4	479 (18.3)	2446 (19.8)	0.04
5	458 (17.5)	2381 (19.3)	0.05
Rural residence	419 (16.0)	1812 (14.7)	0.04
Comorbidities			
Mean (SD) No of unique drugs prescribed in previous year	21.0 (8.7)	12.8 (7.8)	1.03
Atrial fibrillation	348 (13.3)	1174 (9.5)	0.12
Coronary artery bypass grafting surgery	121 (4.6)	302 (2.4)	0.13
Cancer	286 (10.9)	690 (5.6)	0.22
Chronic renal insufficiency	590 (22.5)	569 (4.6)	0.69
Diabetes	1413 (53.9)	6561 (53.2)	0.01
Drugs used in previous year			
Angiotensin converting enzyme inhibitors	1547 (59.0)	5346 (43.3)	0.32
Angiotensin receptor blockers	824 (31.4)	2957 (24.0)	0.17
Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins)	1682 (64.1)	6489 (52.6)	0.23
Clopidogrel	464 (17.7)	922 (7.5)	0.36
Warfarin	1053 (40.1)	1737 (14.1)	0.69
Acetylsalicylic acid/dipyridamole	58 (2.2)	264 (2.1)	0
Hormone replacement therapy	27 (1.0)	83 (0.7)	0.04
Low molecular weight heparin	57 (2.2)	121 (1.0)	0.11
Diuretics	2345 (89.4)	6070 (49.2)	0.85
Diuretics, potassium sparing	592 (22.6)	918 (7.4)	0.51
Calcium channel blocker	1412 (53.8)	4748 (38.5)	0.31
History of outcome			
Congestive heart failure	355 (13.5)	1041 (8.4)	0.18

All cells with values of 5 or less are reported as ≤5 for privacy reasons.

*Up to 5 controls were matched to each case on age (± 1 year), sex, diabetes, and history of outcome.

†Difference between cases and controls divided by pooled standard deviation of two groups; standardised differences <0.1 indicate good balance between groups.

Figures

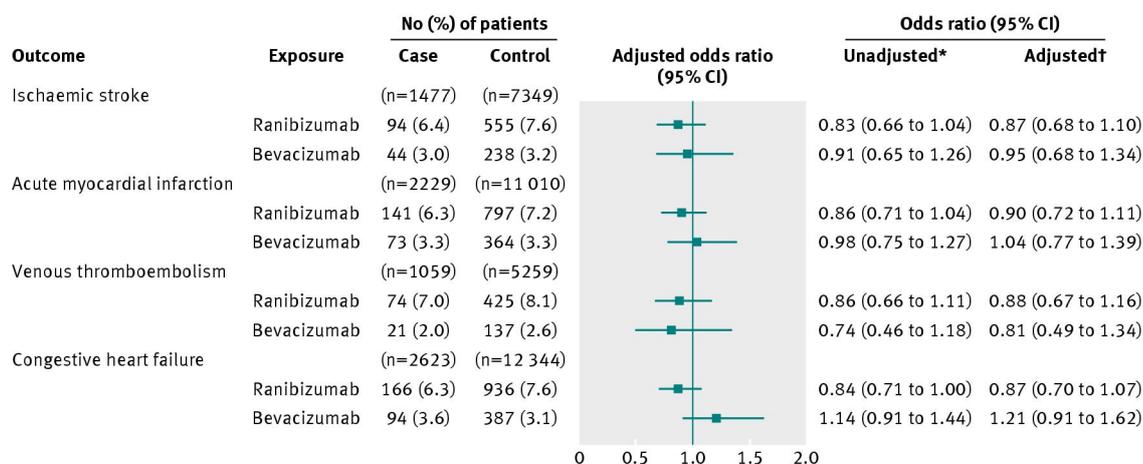


Fig 1 Adverse events after intravitreal injections of vascular endothelial growth factor inhibitors. *Matched on age, sex, history of outcome, and diabetes. †Matched on age, sex, history of outcome, and diabetes; adjusted for: ischaemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, cancer in previous 5 years, clopidogrel, hypertension, chronic renal insufficiency, warfarin; acute myocardial infarction—digoxin, ACE inhibitors, cancer in previous 5 years, clopidogrel, diuretics (regular), hypertension, No of unique prescriptions, chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; venous thromboembolism—digoxin, glaucoma therapies, ACE inhibitors, cancer in previous 5 years, diuretics (potassium sparing), diuretics (regular), low molecular weight heparin, No of unique prescriptions, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), hypertension, chronic renal insufficiency, warfarin

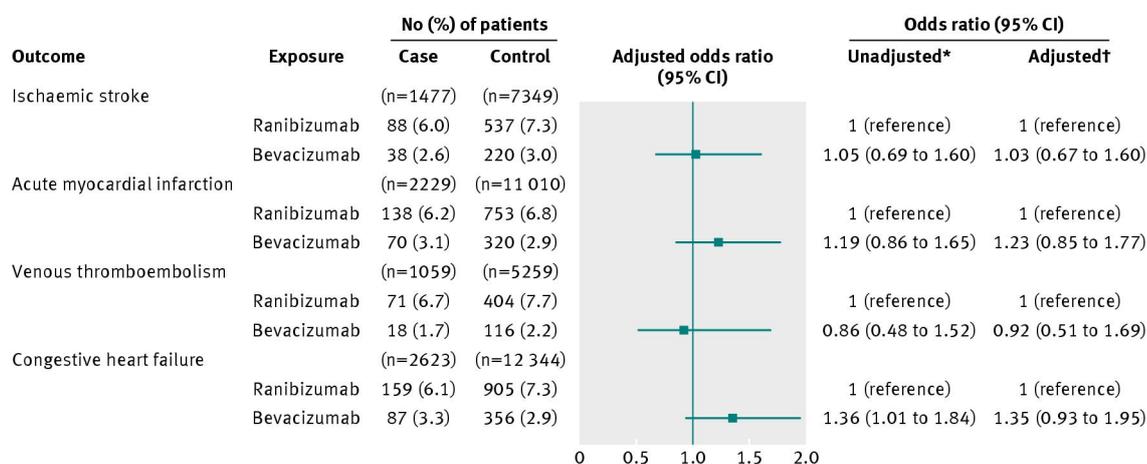


Fig 2 Risk of adverse events among exclusive users of bevacizumab or ranibizumab. *Matched on age, sex, history of outcome, and diabetes. †Matched on age, sex, history of outcome, and diabetes; adjusted for: ischaemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, cancer in previous 5 years, clopidogrel, hypertension, chronic renal insufficiency, warfarin; acute myocardial infarction—digoxin, ACE inhibitors, cancer in previous 5 years, clopidogrel, diuretics (regular), hypertension, chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; venous thromboembolism—digoxin, glaucoma therapies, ACE inhibitors, cancer in previous 5 years, diuretics (potassium sparing), diuretics (regular), low molecular weight heparin, No of unique prescriptions, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), hypertension, income fifth, No of unique prescriptions

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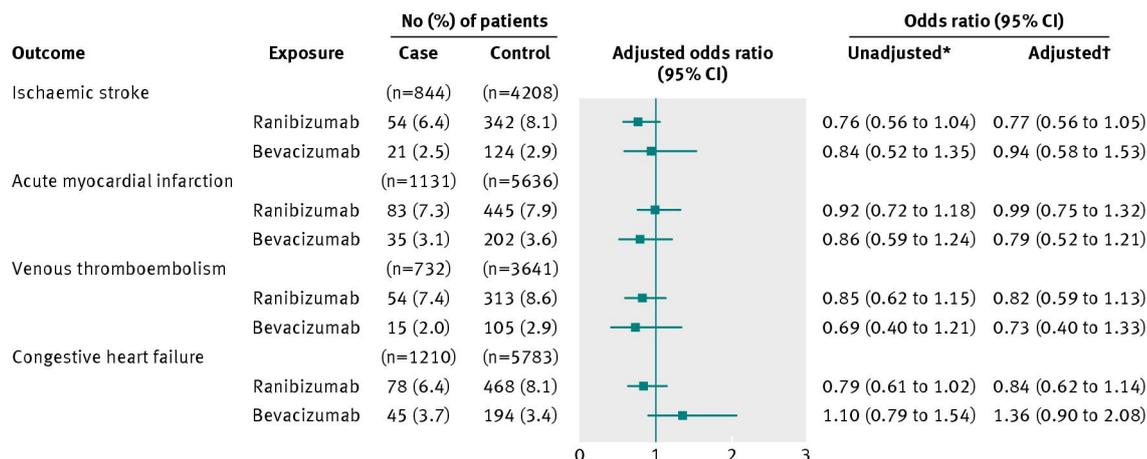


Fig 3 Adverse events after intravitreal injections of vascular endothelial growth factor inhibitors in patients without diabetes. *Matched on age, sex, history of outcome, and diabetes. †Matched on age, sex, history of outcome, and diabetes; adjusted for: ischaemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, cancer in previous 5 years, clopidogrel, hypertension, chronic renal insufficiency, warfarin; acute myocardial infarction—digoxin, ACE inhibitors, cancer in previous 5 years, clopidogrel, diuretics (regular), hypertension, No of unique prescriptions, chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; venous thromboembolism—digoxin, glaucoma therapies, ACE inhibitors, cancer in previous 5 years, diuretics (potassium sparing), diuretics (regular), low molecular weight heparin, No of unique prescriptions, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), hypertension, chronic renal insufficiency, warfarin

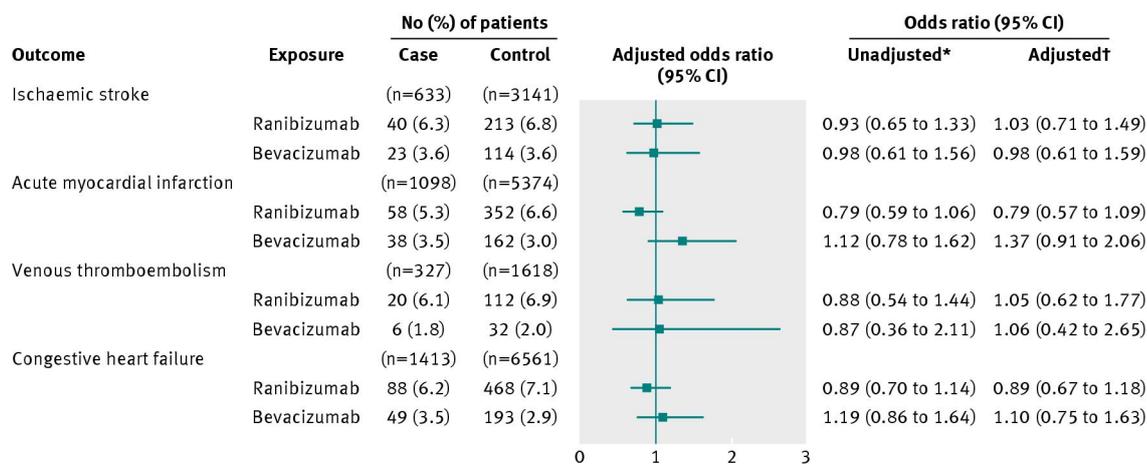


Fig 4 Adverse events after intravitreal injections of vascular endothelial growth factor inhibitors in patients with diabetes. *Matched on: age, sex, history of outcome, and diabetes. †Matched on age, sex, history of outcome, and diabetes; adjusted for: ischaemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, cancer in previous 5 years, clopidogrel, hypertension, chronic renal insufficiency, warfarin; acute myocardial infarction—digoxin, ACE inhibitors, cancer in previous 5 years, clopidogrel, diuretics (regular), hypertension, No of unique prescriptions, chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; venous thromboembolism—digoxin, glaucoma therapies, ACE inhibitors, cancer in previous 5 years, diuretics (potassium sparing), diuretics (regular), low molecular weight heparin, No of unique prescriptions, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), hypertension, chronic renal insufficiency, warfarin

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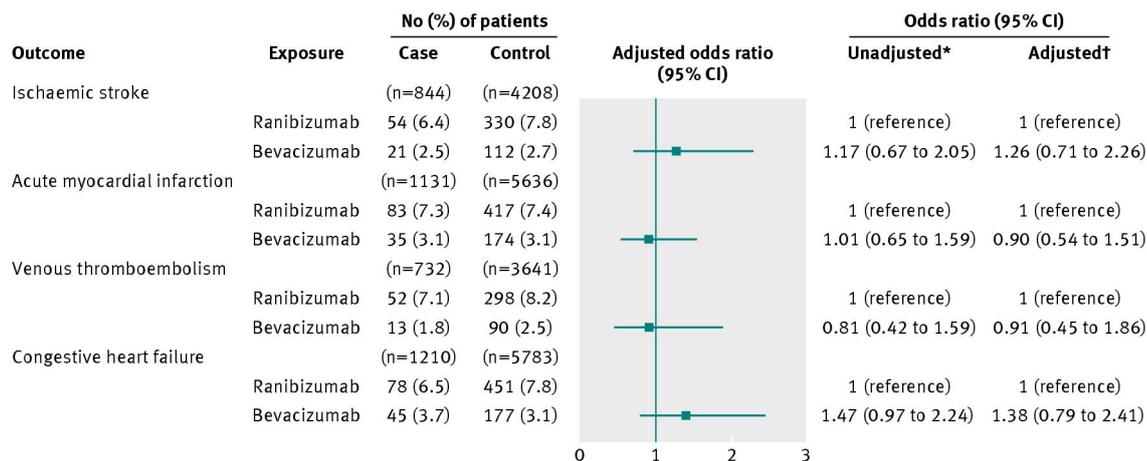


Fig 5 Risk of adverse events in exclusive users of bevacizumab or ranibizumab among patients without diabetes. *Matched on age, sex, history of outcome, and diabetes. †Matched on age, sex, history of outcome and diabetes; adjusted for: ischaemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, angiotensin receptor blockers, cancer in previous 5 years, clopidogrel, chronic renal insufficiency, warfarin; acute myocardial infarction—ACE inhibitors, clopidogrel, chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, No of unique prescriptions; venous thromboembolism—digoxin, glaucoma therapies, cancer in previous 5 years, diuretics (potassium sparing), oestrogen, low molecular weight heparin, No of unique prescriptions, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), hypertension, income quintile, number of unique prescriptions, chronic renal insufficiency, warfarin, photodynamic therapy in previous 180 days, age

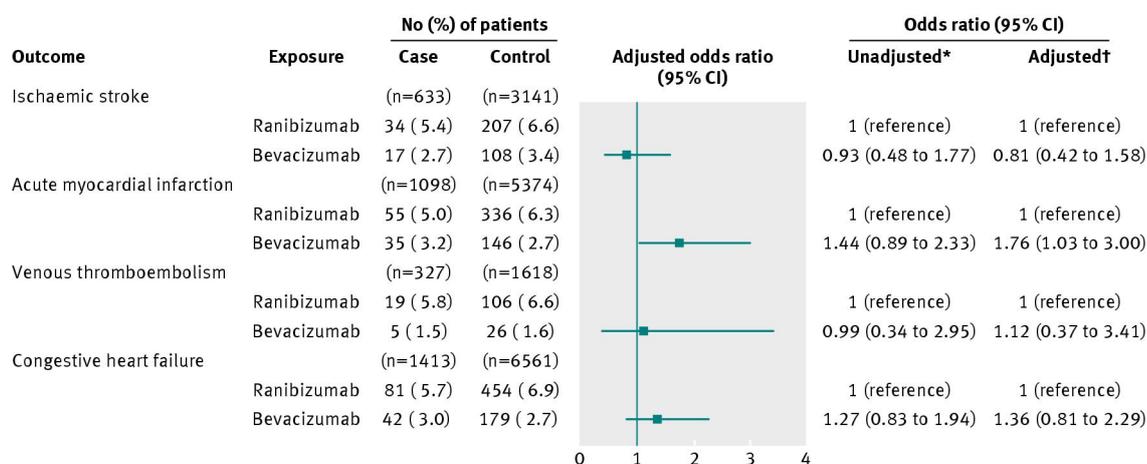


Fig 6 Risk of adverse events in exclusive users of bevacizumab and ranibizumab among patients with diabetes. *Matched on age, sex, history of outcome, and diabetes. †Matched on age, sex, history of outcome, and diabetes; adjusted for: ischaemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, cancer in previous 5 years, clopidogrel, hypertension, chronic renal insufficiency, warfarin; acute myocardial infarction—ACE inhibitors, cancer in previous 5 years, clopidogrel, diuretics (regular), chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin, No of unique prescriptions; venous thromboembolism—cancer in previous 5 years, clopidogrel, low molecular weight heparin, No of unique prescriptions, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), photodynamic therapy in previous 180 days, No of unique prescriptions, chronic renal insufficiency, warfarin

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