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ORIGINAL RESEARCH

Cardiovascular Outcomes with Intravitreal Anti-Vascular Endothelial Growth Factor Therapy in Patients with Diabetes: A Real-World Data Analysis

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ABSTRACT

Background: Anti-vascular endothelial growth factor (anti-VEGF) therapy is commonly used intravitreally for diabetic proliferative retinopathy, but when used systemically for treating cancers, an excess of cardiovascular disease (CVD) events has been noted. The latter is of concern for people with diabetes, who are at higher risk of CVD. This study aims to explore the relationship between incident CVD and intravitreal anti-VEGF therapy in patients with diabetes, compared to other therapies, using a large real-world global federated dataset.

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Methods: Data were analysed using TriNetX, a global electronic medical real-world ecosystem. The study included adults with diabetes and excluded those with a history of CVD prior to the time window of data extraction. Patients were categorised into two cohorts: anti-VEGF therapy or control cohort (laser or steroid therapies). The cohorts were 1:1 propensity score-matched for age, sex, ethnicity, body mass index, systolic blood pressure, HbA1c, and cardiovascular medications. Outcomes analysed at 1, 6 and 12 months were: (1) mortality; (2) acute myocardial infarction (MI); (3) cerebral infarction; and (4) heart failure. Relative risk analyses were performed using the built-in R statistical computing platform on TriNetX.

Results: In patients with diabetes (n=2205; mean age 58.8±15.8, Std diff 0.05; 56% male), anti-VEGF therapy was associated with a numerical but non-statistically significant increased CVD risk over 1, 6, and 12 months: Mortality over 1 month (RR 1; 95% CI 0.42, 2.40), 6 months (RR 1.46; 95% CI 0.72, 2.95) and 12 months (RR 1.41; 95% CI 0.88, 2.27). There was no excess of acute MI over 1 (RR n/a: not applicable; 0/0: 0 events in the anti-VEGF group/0 events in the control group), 6 and 12 months (RR n/a; 0/10 events); cerebral infarction over 1, 6 months (RR n/a; 0/0 events), and 12 months (RR n/a; 0/10); and heart failure over 1 month (RR n/a; 0/0 events), 6 months (RR 1; 95% CI 0.42, 2.40) and 12 months (RR 1; 95% CI 0.42, 2.34).

Conclusions: There was no statistically significant risk of cardiovascular-related events in the short or medium term in patients with diabetes who received intravitreal anti-VEGF therapy, despite a small increase in the number of CVD events. Our study supports the real-world safety of intravitreal anti-VEGF therapy in patients with diabetes free of baseline CVD.

Keywords: Anti-VEGF; Aflibercept; Bevacizumab; Brolucizumab; Faricimab; Acute myocardial infarction; Stroke; Cerebral infarction; Heart failure; TriNetX

Key Summary Points

The cardiovascular safety profile of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is unclear in patients with diabetes, who are susceptible to higher risks of cardiovascular complications.

The present study assesses the real-world links between incident short-to-medium-term cardiovascular disease (CVD) and intravitreal anti-VEGF therapy in patients with diabetes.

Our study shows that intravitreal anti-VEGF is associated with a numerical but non-statistically significant increased risk of cardiovascular events in patients with diabetes over 12 months, compared to other therapies.

Our study supports the safety of anti-VEGF therapy in patients with diabetes free of CVD at baseline.

INTRODUCTION

Intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF) agents have revolutionised the treatment of many ophthalmic pathologies, including diabetic macular oedema and wet age-related macular degeneration (AMD), and they have been shown to be more effective and beneficial than laser or steroid treatments alone in treating these conditions [1–4]. Currently, four widely used anti-VEGF agents in the ophthalmology field are ranibizumab, bevacizumab, aflibercept, and faricimab, which work primarily by binding to VEGF protein directly and impeding its action [5].

VEGF-A, in particular, contributes to the formation of new blood vessels, or angiogenesis, which is essential for tissue development and function and implicated in pathological conditions [6]. Increased VEGF expression is a crucial

factor in the pathogenesis of many ocular diseases, including neovascular AMD, diabetic retinopathy (DR)/macular oedema (DMO), retinal vein occlusion (RVO), glaucoma and retinopathy of prematurity [7]. The increased VEGF production and transcription are thought to be induced by hypoxia, which in turn promotes angiogenesis to restore tissue oxygen supply. However, these new vessels bleed and fibrose easily, leading to complications such as retinal detachment and haemorrhage. VEGF-A also causes inflammation and vascular barrier breakdown, leading to atrophy of the choriocapillaris and degeneration of photoreceptors [8]. In the past decade, anti-VEGF therapy, initially used to suppress tumour growth in cancer treatment, has been re-labelled to treat neovascular eye disease. In addition to inhibiting neovascularisation, anti-VEGF agents have been demonstrated to induce regression of pathological microvessels, stabilise normal vessels and prevent leakage and the concomitant inflammatory response [5].

Systemically delivered anti-VEGF therapy, bevacizumab in particular, has been widely reported to be linked to a variety of cardiovascular adverse events, including acute myocardial infarction (MI), stroke, and heart failure (HF) [5, 9–11]. Nevertheless, not all studies demonstrate this excess risk [12]. Inhibition of VEGF-A decreases the production of nitric oxide and prostaglandin-I 2, leading to vasoconstriction and hypertension. Vascular endothelial death caused by anti-VEGF also causes phospholipids to accumulate on the luminal plasma membrane, facilitating thromboembolic events [13].

However, the risk of cardiovascular adverse events with intravitreally delivered anti-VEGF is not clear. A large meta-analysis found that intravitreal anti-VEGF therapy was not associated with an increase in major cardiovascular events; however, there was a possible signal for mortality risk in patients with diabetic retinopathy (OR, 1.80; 95% CI, 1.03–3.16;) [14]. Given the suspected relatively low occurrence of cardiovascular adverse events with intravitreal anti-VEGF, clinical trials lack sufficient power to assess such risks as secondary endpoints. Understanding the risk of cardiovascular events of anti-VEGF therapy is relevant, particularly in patients with diabetes who are at higher risk of cardiovascular disease (CVD), to support clinicians and patients in making informed healthcare choices.

This study aimed to determine incident short-to-medium-term CVD in relation to intravitreal anti-VEGF therapy in patients with diabetes, compared to other therapies, using a large real-world global federated dataset.

METHODS

Data

Data were utilised from TriNetX, an electronic global federated health research network of 108 large healthcare organisations (HCOs) across 16 countries (predominately US healthcare data). As part of the data ingestion process, when HCOs join the network, data are mapped to a common data model to reflect individual institution, country and regional standards with regard to electronic health record data. All data collection, processing and transmission are performed in compliance with all Data Protection laws applicable to the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons regarding the processing of personal data and the Health Insurance Portability and Accountability Act, the US federal law, which protects the privacy and security of healthcare data. Analytics are performed at the HCOs with only aggregate results being surfaced and returned to the TriNetX platform. Data usage and publication agreements are in place with all HCOs. The TriNetX platform provides access to real-time, real-world electronic medical records, including diagnoses, procedures, medications, laboratory values and genomic information. The TriNetX platform is described in detail elsewhere [15, 16].

Cohort Building

The current study searched for all patients aged 18 years old and over as of the 9th of November 2023 ($n = 110{,}048{,}154$). Of these, patients with diabetes mellitus (ICD-10-CM E08-E13) were included, which consists of type 1, type

2, drug-induced and secondary causes. Patients with a history of CVD, i.e. acute myocardial infarction (MI) (ICD-10-CM I21), cerebral infarction (ICD-10-CM I63) or heart failure (HF) (ICD-10-CM I50) were excluded. Patients with at least one year of data after the index event were included. Patients were then categorised into two cohorts: (1) those who received intravitreal anti-VEGF therapy or (2) alternative therapies. Intravitreal anti-VEGF treatments included all the available intravitreal anti-VEGF agents in the database, which were bevacizumab ($n=73,343$), aflibercept ($n=21,022$), ranibizumab ($n=6111$), brolucizumab ($n=101$), and faricimab ($n=57$). Control (comparator) treatments included photocoagulation of the retina, intravitreal steroid injection, or implants of fluocinolone and dexamethasone. This cohort was chosen so that patients with diabetes free of CVD would be compared. Triamcinolone was excluded because there was no coding specifically for its intravitreal injections, and its administration route could not be determined.

Index Event/Propensity-Score Matching

The index event is the time point at which data collection began. The index events for this study were defined as first receiving anti-VEGF treatment in cohort 1 or control treatment in cohort 2. The two cohorts for analyses were 1:1 propensity score-matched (PSM) for age, sex, ethnicity, body mass index ($<$ or ≥ 25 kg/m^2), systolic blood pressure ($<$ or ≥ 140 mmHg), HbA1c ($<$ or $\geq 7\%$), and cardiovascular medications (digoxin, beta-blockers, alpha-blockers, calcium channel blockers, antianginals, antiarrhythmics, anti-lipid agents, antihypertensives, peripheral vasodilators, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II inhibitor and direct renin inhibitor). TriNetX performed a logistic regression utilising the scikit-learn package in Python version 3.7. Nearest-neighbour matching with a tolerance level of 0.01 and the difference between propensity scores ≤ 0.1 was used.

Outcome Comparison and Statistical Analysis

Outcomes analysis results were calculated in the TriNetX platform using R's Survival package v3.2–3 and validating those results with output from SAS version 9.4. Four outcomes were measured: (1) all-cause mortality and diagnoses of (2) acute MI, (3) cerebral infarction, and (4) HF. Outcome comparisons were made over 1 month, 6 months and 12 months from the index event. The relative risks (RR) were used to estimate the probability of the outcome at the respective time interval, and 95% confidence intervals (CIs) are presented. The t test and X^2 statistical testing were conducted for differences in outcomes between cohorts. A p value <0.05 was considered statistically significant.

RESULTS

A total of 5,821,858 patients with diabetes were identified without a history of CVD. Of these, 24,060 (0.41%) received anti-VEGF treatment, and 2680 (0.05%) received alternative treatments (Fig. 1). In the anti-VEGF treatment group, there were 17,737 (73.7%) patients with type 2 diabetes and 2573 (10.7%) with type 1 diabetes. Within the control group, there were 1581 (59%) with type 2 diabetes and 375 (14%) with type 1 diabetes. After 1:1 propensity matching, the number of patients in both groups reduced to 2205. No patients were censored from either 1-month, 6-month or 12-month analyses. A summary of propensity score-matching (PSM) characteristics is summarised in Table 1.

All-Cause Mortality

There were numerical but non-statistically significant differences in the risk of all-cause mortality over 1 month (RR 1; 95% CI 0.42,2.40), 6 months (RR 1.57; 95% CI 0.91,2.71) and 12 months (RR 1.28, 95% CI 0.90,1.83) between the anti-VEGF and control groups.

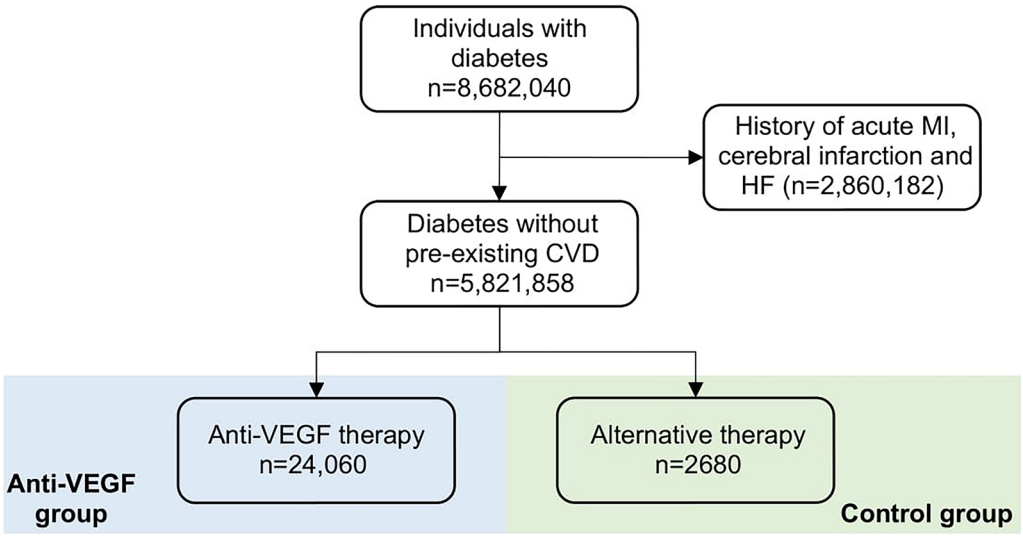

Fig. 1 Patient selection. Individuals with diabetes without pre-existing cardiovascular disease (CVD) received anti-vascular endothelial growth factors (anti-VEGF) therapy or alternative therapy. *MI* myocardial infarction, *HF* heart failure

Table 1 Patient characteristics before and after propensity score matching (PSM)

Characteristic	Before PSM			After PSM		
	Anti-VEGF ($n = 24{,}060$)	Control ($n = 2680$)	Std. diff	Anti-VEGF ($n = 2205$)	Control ($n = 2205$)	Std. diff
Age at index event (years)	60.1 ± 14.7	59.6 ± 15	0.04	58.8 ± 15.8	59.6 ± 15.6	0.05
Sex (male) (%)	50	57	0.14	56	55	0.03
Race – white (%)	61	74	0.28	74	74	0.01
Black or African American (%)	14	4	0.39	4	4	0.02
Asian (%)	4	10	0.23	7	6	0.03
Cardiovascular medications	70	21	1.12	25	25	0.00
BMI (kg/m^2)	30.1 ± 6.7	30.4 ± 6.82	0.06	29.7 ± 6.04	30.5 ± 6.87	0.13
Systolic blood pressure (mmHg)	137 ± 21.8	139 ± 22.3	0.14	135 ± 21.2	132 ± 19	0.12
HbA1c (mmol/mol)	8.11 ± 2.19	7.31 ± 1.79	0.42	7.9 ± 2.21	7.22 ± 1.85	0.33

Anti-VEGF anti-vascular endothelial growth factor, *Std. diff.* the standardised difference of mean, *BMI* body mass index
Continuous data are expressed as mean ± standard deviation, and categoric data is expressed as *n* (%)

Acute Myocardial Infarction

No events of acute MI were found in either group over 1 month (RR n/a). There were ten events in each group over 6 months, with no differences in the risk of acute MI (RR 1; CI 95% 0.42, 2.40). The incidence of acute MI did not change over 12 months (RR 1; CI 95% 0.42, 2.40) between the anti-VEGF and control groups.

Outcomes (n)	1 month		
	Anti-VEGF	Control	RR (95% CI)
All-cause mortality	10	10	1 (0.42,2.40)
Acute MI	0	0	-
Cerebral infarction	0	10	-
Heart failure	0	0	-
Outcomes (n)	**6 months**		
	Anti-VEGF	**Control**	**RR (95% CI)**
All-cause mortality	33	21	1.57 (0.91,2.71)
Acute MI	10	10	1 (0.42,2.40)
Cerebral infarction	0	10	-
Heart failure	10	10	1 (0.42,2.40)
Outcomes (n)	**12 months**		
	Anti-VEGF	**Control**	**RR (95% CI)**
All-cause mortality	68	53	1.28 (0.9,1.83)
Acute MI	10	10	1 (0.42,2.40)
Cerebral infarction	0	10	-
Heart failure	10	10	1 (0.42,2.40)

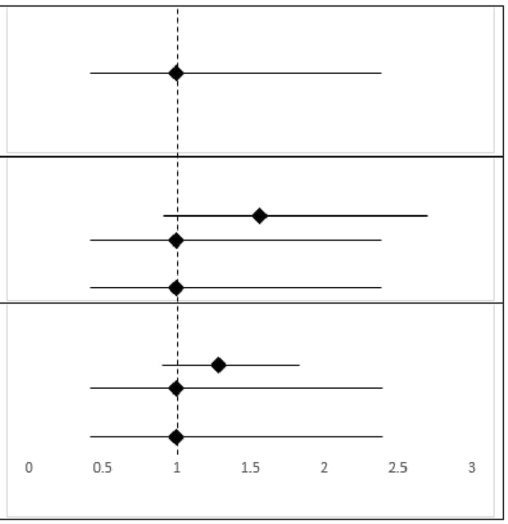

Fig. 2 Summary of cardiovascular outcomes with anti-vascular endothelial growth factor (anti-VEGF) therapy in patients with diabetes over 1, 6 and 12 months. *RR* relative risk, *CI* confidence interval, *MI* myocardial infarction. Data expressed the number of outcomes and relative risk (95% confidence interval)

Cerebral Infarction

There were no events of cerebral infarction in the anti-VEGF group but ten events in the control group over 1 month (RR n/a). The incidences remained the same over 6 and 12 months (RR n/a).

Heart Failure

There were no events of HF in either group over 1 month (RR n/a). There were ten events in each group over 6 months, with no difference in the risk of heart failure (RR 1; 95% CI 0.42, 2.40). The incidence of HF did not change over 12 months (RR 1; 95% CI 4.42, 2.40) between the anti-VEGF and control groups (Fig. 2).

DISCUSSION

In this study, we have conducted a real-world retrospective propensity-matched cohort analysis to evaluate the putative association between cardiovascular events and intravitreal anti-VEGF therapy in patients with diabetes. Our study demonstrates that intravitreal anti-VEGF therapy is not associated with a significantly increased risk of cardiovascular events in patients with diabetes over 12 months.

Intravitreal anti-VEGF therapy has become a pillar of treatment for multiple eye conditions in recent years. Until now, their real-world safety profile in patients with diabetes has been unclear. Previously, there were also concerns that there may be greater susceptibility to cardiovascular events/complications [14].

A number of studies have evaluated the systemic adverse effects of intravitreal anti-VEGF therapy. However, the overall results are conflicting: a 2018 Cochrane review of 24 trials with 6007 patients with diabetes and DMO found intravitreal anti-VEGF therapy was not associated with increased risk of death with aflibercept (RR 1.01, 95% CI 0.34,3.03), bevacizumab (RR 1.61, 95% CI 0.45, 5.69) and pegaptanib (RR 0.81, 95% CI 0.16,4.03), and ranibizumab (RR 0.90, 95% CI 0.40, 2.01); there was also no increased risk of thromboembolic events at 24 months with any of the anti-VEGF drugs compared to the control group (alternative treatment, sham or no treatment). However, the analysis was incoherent, and the evidence was considered to be of low or very low certainty [17].

In contrast, a meta-analysis of four trials (n = 1328) has shown that those receiving maximum monthly doses of intravitreal anti-VEGF in DMO had an increased risk of death (OR 2.57, 95% CI 1.31,5.05) and cerebrovascular events (OR 2.33, 95% CI 1.04,5.22) but no increased risks of MI or arteriothrombotic events, compared with those receiving sham injections and laser treatments [18]. The regularity and frequency of the anti-VEGF administration in this study design are more relevant to clinical practice. Increased risk of stroke was also demonstrated in a review of five trials of ranibizumab compared to control (HR 2.2, 95% CI 0.80, 7.10). Further sensitivity analysis in a high-risk subgroup of patients, which included patients aged over 85 with a history of stroke or transient ischaemic attack, demonstrated increased risk (HR 2.12, 95% CI 0.75, 5.90) [18].

Inconsistent findings in the literature may be due to the differences in study design. Some trials do not exclude patients with a history of cardiovascular disease, which could lead to a higher occurrence of adverse events. Further, the anti-VEGF drugs and their dosage were also varied between studies. Overall, the incidence of adverse events was low among studies, and the CIs were wide. Additionally, most studies are likely underpowered to accurately detect differences in risks of intravitreal anti-VEGF, even if they exist.

It is well established that anti-VEGF therapy may enter the circulation when administrated intravitreally [5]. Plasma VEGF levels were shown to be reduced by bevacizumab and aflibercept after 7 days and 1 month in patients with AMD; however, no significant reductions of plasma VEGF levels were observed in patients receiving ranibizumab during follow-up compared to the other two anti-VEGF drugs [19]. Ranibizumab has a smaller molecular size and lacks Fc domain, leading to a different pharmacokinetic profile than other anti-VEGF agents [20]. These findings suggest that the distinctive anti-VEGF agents may influence the free VEGF levels differently.

In addition to angiogenesis, VEGF-A is important for cardiac morphogenesis, contractility and remodelling of the myocardium. Depletion of VEGF in animal models has been shown to lead to impaired myocardial angiogenesis with subsequent heart failure [21]. In patients who experienced MI, low plasma VEGF levels were found to be associated with a significantly increased risk for further major adverse cardiovascular and cerebrovascular events [22]. This paradoxical finding makes predicting anti-VEGF's adverse effects challenging. The pharmacodynamic-pharmacokinetic profiles of anti-VEGF therapy appear to be complex and not well understood. Since most patients would require repeated injections for chronic VEGF inhibition, further longer-term studies with robust treatment regimens are needed to reflect the risk of cardiovascular in patients with diabetes receiving serial or long-term anti-VEGF therapy.

Strengths

Our study includes a large number of patients from a real-world database, potentially enhancing statistical power and generalisability. We also used propensity matching against appropriated patient characteristics and cardiovascular phenotype to address significant potential confounding factors.

Limitations

Our study is limited by the coding system of the platform. We could only select inclusion and exclusion criteria based on the ICD-10 codes. The respective indications for intravitreal injections were not reported. Given the limited event rate in the overall analysis, a sub-analysis of different types of diabetes and specific anti-VEGF agents was not undertaken. The details of the eye disease, such as type, duration, and severity, could not be entirely determined. The tobacco use was also not propensity-score matched as

data availability for this variable was more limited. The index event was set as the initiation of either anti-VEGF agents or control treatment, however we could not determine the dose or frequency of the injections. Another source of uncertainty is that patients could have received cross-over therapies after the index event and additionally we are unable to account for residual effect from unknown confounders.

CONCLUSIONS

There was no statistically significant risk of cardiovascular-related events in the short or medium term in patients with diabetes who received intravitreal anti-VEGF therapy, despite a very small increase in the number of CVD events. Our study supports the real-world safety of intravitreal anti-VEGF therapy in patients with diabetes free of baseline CVD.

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Author Contribution. Jonathan Y M Lai: Generated the results and analysed data using the TriNetX platform, drafted and edited the manuscript. David R Riley and Matthew Anson: involved in data analysis and reviewed the manuscript. Alex Henney, Daniel J Cuthbertson, Gregory Y H Lip, Sizheng Steven Zhao, Timothy L Jackson, Katarzyna Nabrdalik: reviewed and edited the manuscript and provided methodological input. Gema Hernadez and Philip Austin: aided in the generation of the results and data analysis/methodology on the TriNetX platform. Uazman Alam: Conceptualised the study, reviewed and edited the manuscript, and provided supervision.

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Data Availability. To gain access to the data in the TriNetX research network, a request can be made to TriNetX (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary and no patient identifiable information can be obtained. No data from Liverpool University NHS Foundation Trust were utilised in this analysis.

Declarations

Conflict of Interest. Daniel J Cuthbertson has received investigator-initiated grants from Astra Zeneca and Novo Nordisk and support for education from Perspectum; Gema Hernadez and Philip Austin are employees of TriNetX LLC; Gregory Y H Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871; Timothy L Jackson is a consultant/advisor to 2CTech; Alcon; Dutch Ophthalmic Research Centre; iLumen; Opthea; Outlook Therapeutics; Oxurion; Regeneron. His NHS employer receives site fees for patients enrolled on commercial retinal trials of conditions treated by anti-VEGF therapy. Oraya/Zeiss provided free use of device for NIHR-funded RCT; Bayer provided free provision and distribution of Eylea for Euretina/Fight for Sight funded trial; Uazman Alam has received honoraria from Procter & Gamble, Viatris, Grunenthal, Eli Lilly and Sanofi for educational meetings. UA has also received investigator-led funding by Procter & Gamble; Jonathan Y M Lai, David R Riley, Matthew Anson, Alex Henney, Sizheng Steven Zhao, and Katarzyna Nabrdalik declare no conflicts of

interest to declare. Uazman Alam is an Editorial Board member of Diabetes Theray. Uazman Alam was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. All data collection, processing and transmission are performed in compliance with all Data Protection laws applicable to the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons regarding the processing of personal data and the Health Insurance Portability and Accountability Act, the US federal law, which protects the privacy and security of healthcare data. Ethics approval was not required. Permission to access and publish data from this study was granted by TriNetX LLC.

REFERENCES

1. Régnier S, Malcolm W, Allen F, Wright J, Bezlyak V. EFficacy of anti-VEGF and laser photocoagulation in the treatment of visual impairment due to diabetic macular edema: a systematic review and network meta-analysis. PLoS One 2014;9. https://doi.org/10.1371/journal.pone.0102309.

2. Qian T, Zhao M, Xu X. Comparison between anti-VEGF therapy and corticosteroid or laser therapy for macular oedema secondary to retinal vein occlusion: a meta-analysis. J Clin Pharm Ther 2017;42. https://doi.org/10.1111/jcpt.12551.

3. Rajendram R, Fraser-Bell S, Kaines A, Michaelides M, Hamilton RD, Esposti SD, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: Report 3. Arch Ophthalmol 2012;130. https://doi.org/10.1001/archophthalmol.2012.393.

4. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017;237. https://doi.org/10.1159/000458539.

5. Fogli S, Del Re M, Rofi E, Posarelli C, Figus M, Danesi R. Clinical pharmacology of intravitreal anti-VEGF drugs. Eye 2018;32. https://doi.org/10.1038/s41433-018-0021-7.

6. Penn JS, Madan A, Caldwell RB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008;27. https://doi.org/10.1016/j.preteyeres.2008.05.001.

7. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye 2013;27. https://doi.org/10.1038/eye.2013.107.

8. Pozarowska D, Pozarowski P. The era of anti-vascular endothelial growth factor (VEGF) drugs in ophthalmology, VEGF and anti-VEGF therapy. Cent Eur J Immunol 2016;41. https://doi.org/10.5114/ceji.2016.63132.

9. Hwang DJ, Kim YW, Woo SJ, Park KH. Comparison of systemic adverse events associated with intravitreal anti-VEGF injection: ranibizumab versus bevacizumab. J Korean Med Sci 2012;27. https://doi.org/10.3346/jkms.2012.27.12.1580.

10. Jiang L, Ping L, Yan H, Yang X, He Q, Xu Z, et al. Cardiovascular toxicity induced by anti-VEGF/VEGFR agents: a special focus on definitions, diagnoses, mechanisms and management. Expert Opin Drug Metab Toxicol. 2020. https://doi.org/10.1080/17425255.2020.1787986.

11. Crocetto F, Ferro M, Buonerba C, Bardi L, Dolce P, Scafuri L, et al. Comparing cardiovascular adverse events in cancer patients: a meta-analysis of combination therapy with angiogenesis inhibitors and immune checkpoint inhibitors versus

angiogenesis inhibitors alone. Crit Rev Oncol Hematol 2023;188. https://doi.org/10.1016/j.critrevonc.2023.104059.

12. Chen YC, Yeh LT, Yang SF, Chou MC, Huang JY, Yeh C Bin. Risk of thromboembolic events and major adverse cardiovascular events following antivascular endothelial growth factor therapy in patients with colorectal cancer. Cancers (Basel) 2023;15. https://doi.org/10.3390/cancers15010009.

13. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer 2007;96. https://doi.org/10.1038/sj.bjc.6603813.

14. Ngo Ntjam N, Thulliez M, Paintaud G, Salvo F, Angoulvant D, Pisella P-J, et al. Cardiovascular adverse events with intravitreal anti-vascular endothelial growth factor drugs. JAMA Ophthalmol 2021;139. https://doi.org/10.1001/jamaophthalmol.2021.0640.

15. Riley DR, Essa H, Austin P, Preston F, Kargbo I, Ibarburu GH, et al. All-cause mortality and cardiovascular outcomes with sodium-glucose Co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and with combination therapy in people with type 2 diabetes. Diabetes, Obes Metab 2023;25. https://doi.org/10.1111/dom.15185.

16. Anson M, Zhao SS, Austin P, Ibarburu GH, Malik RA, Alam U. SGLT2i and GLP-1 RA therapy in type 1 diabetes and reno-vascular outcomes: a real-world study. Diabetologia 2023;66. https://doi.org/10.1007/s00125-023-05975-8.

17. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev 2018;2018. https://doi.org/10.1002/14651858.CD007419.pub6.

18. Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. JAMA Ophthalmol 2016;134. https://doi.org/10.1001/jamaophthalmol.2015.4070.

19. Zehetner C, Kirchmair R, Huber S, Kralinger MT, Kieselbach GF. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. Br J Ophthalmol 2013;97. https://doi.org/10.1136/bjophthalmol-2012-302451.

20. Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol 2014;98. https://doi.org/10.1136/bjophthalmol-2014-305252.

21. Braile M, Marcella S, Cristinziano L, Galdiero MR, Modestino L, Ferrara AL, et al. VEGF-A in cardiomyocytes and heart diseases. Int J Mol Sci 2020;21. https://doi.org/10.3390/ijms21155294.

22. Matsudaira K, Maeda K, Okumura N, Yoshikawa D, Morita Y, Mitsuhashi H, et al. Impact of low levels of vascular endothelial growth factor after myocardial infarction on 6-month clinical outcome-results from the Nagoya acute myocardial infarction study. Circ J 2012;76. https://doi.org/10.1253/circj.CJ-11-1127.