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Cardiovascular morbidity and all-cause mortality in patients with retinal vein occlusion: a Danish nationwide cohort study

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ABSTRACT

Background/aims Associations between retinal vein occlusion (RVO) and subsequent cardiovascular disease (CVD) or mortality have not been evaluated in a recent cohort, after novel therapeutic options have increased referrals for treatment of the condition. We aimed to evaluate overall and subtype-stratified risk of CVD and all-cause mortality following RVO and assess any alterations after the introduction of angiostatic therapy in Denmark in 2011.

Methods This nationwide, registry-based cohort study from 1998 to 2018 evaluated 4 194 781 individuals. Hazard ratios (HRs) were reported for RVO as an overall measure and subclassified as branch and central RVO.

Results Patients with RVO (n=15 665) were median 71.8 years old at the time of exposure and 50.7% were women. RVO associated with incident CVD (adjusted HR 1.13, 95% CI 1.09 to 1.17) but not mortality (adjusted HR 1.00, 95% CI 0.97 to 1.03). Almost similar risks of CVD were found for patients with branch and central RVO (adjusted HRs 1.14, 95% CI 1.03 to 1.25, and 1.12, 95% CI 1.00 to 1.25, respectively), but only patients with central RVO exhibited increased mortality (adjusted HR 1.12, 95% CI 1.04 to 1.21). Risk of CVD, especially non-ischaemic, was higher for patients diagnosed after 2011 (adjusted HRs 1.24, 95% CI 1.15 to 1.33 vs 1.06, 95% CI 1.01 to 1.12).

Conclusion In a cohort of the Danish population aged 40 years or more, patients with RVO had a 13% increased risk of incident CVD compared with unexposed individuals. Risk of CVD was increased after 2011, when intravitreal angiostatic treatment was introduced and referral practices altered.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increased risk of different cardiovascular diseases (CVDs) in patients with retinal vein occlusion (RVO) is well established and while most studies find no increased risk of mortality after RVO, results are inconsistent.
⇒ Introduction of intravitreal angiostatic treatment, almost a decade ago, altered referral practices for the treatment of patients, which makes previous findings of subsequent comorbidity and mortality inadequate.

WHAT THIS STUDY ADDS

⇒ In a nationwide cohort, our study finds an increased risk of CVDs in patients with RVO diagnosed after 2011.
⇒ All-cause mortality was increased in patients with CRVO in the overall analysis, but not when diagnosed after 2011, indicating a lower mortality risk than hitherto reported.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The cohort of today's patients with RVO might be in higher risk of CVD than previously described, encouraging clinicians to be continuously aware of cardiovascular evaluation of these patients.

INTRODUCTION

Retinal vein occlusion (RVO) is a sight-threatening retinal disease classified as branch and central retinal vein occlusion (BRVO and CRVO, respectively) according to anatomical location. The most frequently associated risk factors for RVO include arterial hypertension, diabetes, cardiovascular disease (CVD), hypercholesterolaemia, glaucoma, systemic inflammatory diseases and coagulability disorders.[1]

Previously, treatment of RVO included retinal photocoagulation for patients with neovascularisation and BRVO-induced macular oedema. In early 2011, intravitreal vascular endothelial growth factor (VEGF) inhibition for macular oedema in RVO was approved in Europe[2 3] and has largely replaced retinal photocoagulation in most European countries, including Denmark.

While previous studies have reported increased risk of CVD and in some cases increased mortality in patients with RVO,[4 5] these may reflect a different population, as a substantial number of patients with RVO were not referred to hospitals at the time when treatment options were limited. Thus, a contemporary evaluation is important to investigate if the introduction of intravitreal VEGF inhibition and following changes in referral practices have altered risks of incident CVD or all-cause mortality.

AIM

In this Danish nationwide registry-based cohort study, we aimed to evaluate (1) the association between RVO and CVD and all-cause mortality, (2)

any potential differences in risks between BRVO and CRVO and (3) to compare these associations in patients with RVO referred before and after 2011.

METHODS

Data sources

This study was a nationwide, population-based, cohort study based on data from the Danish national registers. The Danish National Patient Registry (DNPR) contains information on all hospitalisations in Denmark since 1977 and outpatient contacts since 1995.[6] Diagnoses have been coded according to the 8th and 10th revision of the International Classification of Diseases (ICD). Data on prescription drugs were acquired from the Danish National Prescription registry.[7] The Civil Registration System contains data on vital status, marital status and migration as well as the unique personal registration number, which allows for linkage between registries.[8]

Study population

The study population was identified, using the civil registration system, as individuals alive and living in Denmark and being or becoming 40 years of age between 1 January 1998 and 31 December 2017. Cohort entry date was 1 January 1998 or, for individuals becoming 40 years of age thereafter, the date of their 40th birthday. The cohort was followed until 31 December 2018.

Exposure

Overall exposure was RVO, identified as individuals registered with any diagnostic code of RVO (online supplemental table 1) with the first diagnosis defining the date of exposure.

Patients were subclassified according to anatomic location of RVO, when available. Individuals registered with both BRVO and CRVO were included in the overall RVO group. Individuals were excluded from the cohort if they had any record of RVO prior to their cohort entry date. To increase the specificity of the exposure, we only accepted those registered with a RVO diagnosis given at ophthalmology-associated hospital departments.

Outcomes

Principal outcomes were CVD and all-cause mortality. CVD was defined by diagnostic codes modified from Hvidberg *et al*.[9]. For secondary outcome analyses, CVD was subclassified as ischaemic CVD (acute myocardial infarction, ischaemic stroke and peripheral arterial disease), non-ischaemic CVD (non-ischaemic heart failure, atrial fibrillation, non-ischaemic stroke and aortic disease) and venous diseases (deep venous thrombosis and pulmonary embolism) (online supplemental table 1 for details). The date of the first registration was considered the date of CVD diagnosis.

We excluded individuals with any previous record of the outcome in question from each analysis.

Most of the included CVDs have been validated in the DNPR.[10–16] Few positive predictive values have been recorded below 80%, including heart failure, peripheral arterial disease and stroke.[10 14–16] Thus, we demanded that these should be given as primary diagnoses (ie, main reason for hospitalisation or outpatient contact) to increase validity.[10 12 14 15]

Lag-time period

We implemented a 90-day lag-time period from RVO exposure to incident CVD to account for undetected CVD, likely to have been present at the time of RVO. During the lag-time period, individuals experiencing a CVD event were censored the day prior to the event.

Covariates

The selection of covariates was guided by a priori knowledge. Covariates included sex (male/female), age at entry (continuous), index year (1998–2017, continuous), marital status at entry (never married, married/cohabiting, widowed), Charlson Comorbidity Index (CCI) conditions as separate dichotomous variables (without diabetes mellitus and chronic obstructive pulmonary disorder (COPD)), arterial hypertension, diabetes mellitus, dyslipidaemia and COPD as a proxy for smoking. All comorbidities were defined by diagnostic codes (online supplemental table 1). In accordance with Hvidberg *et al*,[9] arterial hypertension, diabetes mellitus and dyslipidaemia were defined by diagnostic codes and/or prescription drugs. The comorbidity variables were adjusted for as binary (yes/no) variables at entry and as time-varying covariates during follow-up.

Analysis

To characterise the population by demographic and baseline data, we presented median and quartiles (25% and 75% percentile) for continuous variables and counts and proportions for categorical variables. We reported CCI scores, as counts and percentages of distribution, calculated at study entry.[17 18]

We applied a multivariate Cox proportional hazards model to compare CVD hazards of individuals with RVO to those without RVO, estimating crude, semiadjusted and adjusted HRs with 95% CIs. RVO was included as a time-varying exposure, changing status from unexposed to exposed at first diagnosis of RVO. Number of days since date of origin (date the person turned 40 years of age) was used as the underlying timeline. Individuals were followed until a CVD, death, emigration or end of study period (31 December 2018), whichever occurred first. A semiadjusted model (sex and age at entry) and a fully adjusted model (sex, age at entry, index year, marital status at entry, CCI conditions, diabetes mellitus, arterial hypertension and COPD) were performed. Any CCI conditions that were an outcome of the given model were excluded as covariate.

We reported number of events, median time to event, median age at event, total risk time and event rates.

A test for interaction with sex and age revealed interaction for sex only, and sex-stratified results were reported (online supplemental table 5).

We performed separate subgroup analysis of BRVO and CRVO as exposures in multivariate models identical to the main analysis models.

We performed separate analyses for RVO exposure prior to and after 17 March 2011, the date of approval for VEGF inhibitory treatment for RVO in the European Union, and in subgroups of RVO exposure between 2011–2014 and 2015–2018.

Secondary analyses

To estimate if VEGF inhibitory treatment was an intermediary factor between RVO and the outcomes in question after 2011, we performed a separate fully adjusted model, and stratified patients with RVO according to anti-VEGF treatment (binary, yes/no). Anti-VEGF treatment was defined as any registration of the treatment procedure code in DNPR (ICD10 KCKD05B) prior to an outcome or end of follow-up.

All analyses were carried out using Stata V.17 (Stata, College Station, Texas, USA).

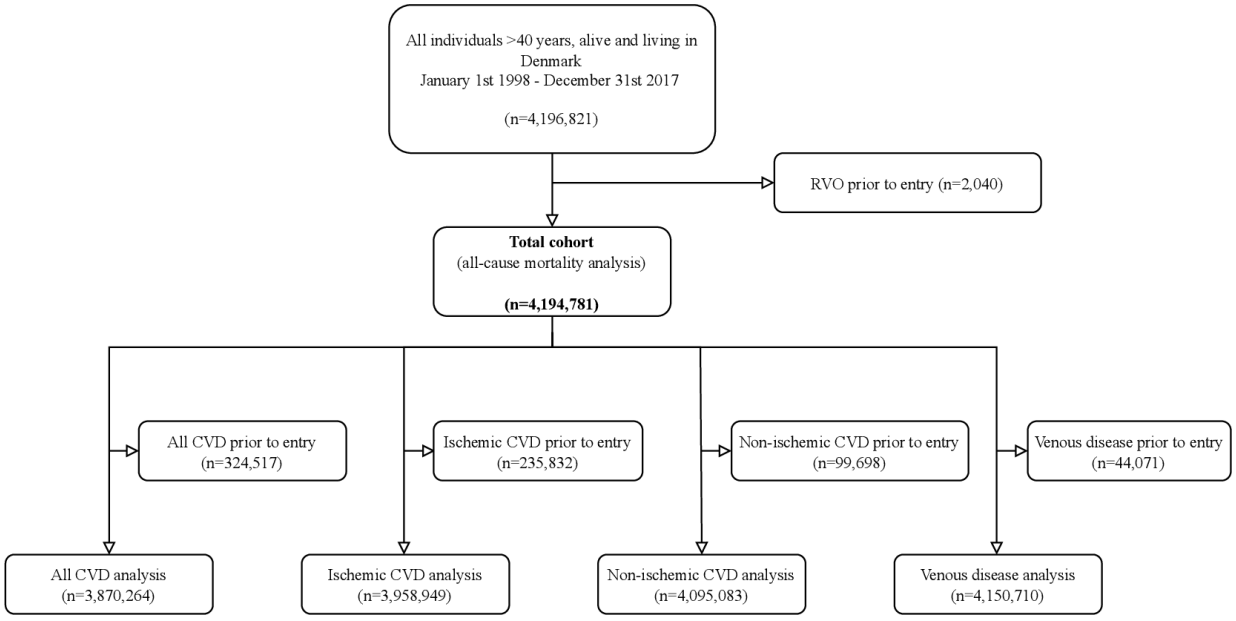

Figure 1 Flowchart of cohort selection. CVD, cardiovascular diseases.

RESULTS

We identified 4 196 821 individuals being or becoming 40 years of age from 1 January 1998 to 31 December 2017. Of these, 2040 individuals had a record of RVO prior to entry date; thus, 4 194 781 unique individuals met our inclusion criteria and comprised the overall cohort (figure 1). In each analysis of CVD and the subgroups' ischaemic CVD, non-ischaemic CVD and venous diseases, we excluded 324 517; 235 832; 99 698 and 44 071 patients, respectively, due to record of one or more of the outcome diagnoses in question, prior to entry date. Median overall follow-up time was 15.5 years.

Evaluation of associations between RVO and CVD and all-cause mortality

Table 1 includes the baseline characteristics of all individuals, and individuals with and without RVO.

Exposed individuals were older at entry and more likely to be diagnosed with arterial hypertension, dyslipidaemia, diabetes mellitus and smoking-related disorders than individuals never exposed to RVO.

The distribution of sex and CCI scores was comparable between groups. Median age at RVO exposure was 71.8 years. After 2011, the mean number of registered patients per year with RVO almost doubled (table 1 and online supplemental figure 1).

RVO exposure was associated with increased risk of incident CVD (adjusted HR 1.13, 95% CI 1.09 to 1.17; figure 2 and online supplemental table 2). Similarly, risk of ischaemic CVD and non-ischaemic CVD was higher in those exposed to RVO, most evidently in non-ischaemic CVD (adjusted HR 1.23, 95% CI 1.15 to 1.33). We found no association with the risk of developing other venous diseases and no association with all-cause mortality (adjusted HRs 0.99, 95% CI 0.90 to 1.09 and 1.00, 95% CI 0.97 to 1.03, respectively).

Evaluation of associations between BRVO and CRVO subgroups and CVD and all-cause mortality

Table 2 includes the baseline characteristics of the BRVO and CRVO subgroups.

Individuals with BRVO were younger at entry, more likely to be women and less likely to be diagnosed with smoking-related disorders than individuals with CRVO. Distribution of CCI scores, arterial hypertension, dyslipidaemia and diabetes was comparable between groups. Median age at BRVO and CRVO exposure was 71.1 versus 73.0 years.

BRVO was associated with increased risk of CVD, ischaemic CVD and non-ischaemic CVD (adjusted HRs 1.14, 95% CI 1.03 to 1.25; 1.18, 95% CI 1.05 to 1.33; and 1.22, 95% CI 1.07 to 1.38, respectively; figure 2 and online supplemental table 2). The tendency was similar in CRVO (adjusted HRs 1.12, 95% CI 1.00 to 1.25; 1.12, 95% CI 0.99 to 1.28; and 1.16, 95% CI 1.00

Table 1 Baseline characteristics of all participants, RVO exposed and never-exposed

	All	RVO exposed	Never exposed
	(N=4 194 781)	(n=15 665)	(n=4,179,116)
Sex			
Men	2 054 446 (49.0)	7729 (49.3)	2 046 717 (49.0)
Women	2 140 335 (51.0)	7936 (50.7)	2 132 399 (51.0)
Age at index date, years	45.6 (40.0–59.9)	58.8 (49.9–67.7)	45.6 (40.0–59.9)
Age at RVO diagnosis, years	71.8 (63.0–79.4)	71.8 (63.0–79.4)	NA
No of incident RVO diagnoses, mean no per year			
1998–2010	547	547	NA
2011–2018	1070	1070	NA
Charlson Comorbidity Index score			
0 (low)	3 781 035 (90.1)	13 961 (89.1)	3 767 074 (90.1)
1	172 558 (4.1)	746 (4.8)	171 812 (4.1)
2	190 059 (4.5)	774 (4.9)	189 285 (4.5)
>3 (high)	51 129 (1.2)	184 (1.2)	50 945 (1.2)
Comorbid conditions			
Arterial hypertension	1 479 292 (35.3)	10 866 (69.4)	1 468 426 (35.1)
Dyslipidaemia	1 067 567 (25.4)	7907 (50.5)	1 059 660 (25.4)
Diabetes	451 372 (10.8)	2913 (18.6)	448 459 (10.7)
Smoking-related disorders	239 047 (5.7)	1569 (10.0)	237 478 (5.7)

Data presented as median (25%–75% percentile) for continuous variables and count (%) for categorical variables.
NA, not applicable; RVO, retinal vein occlusion.

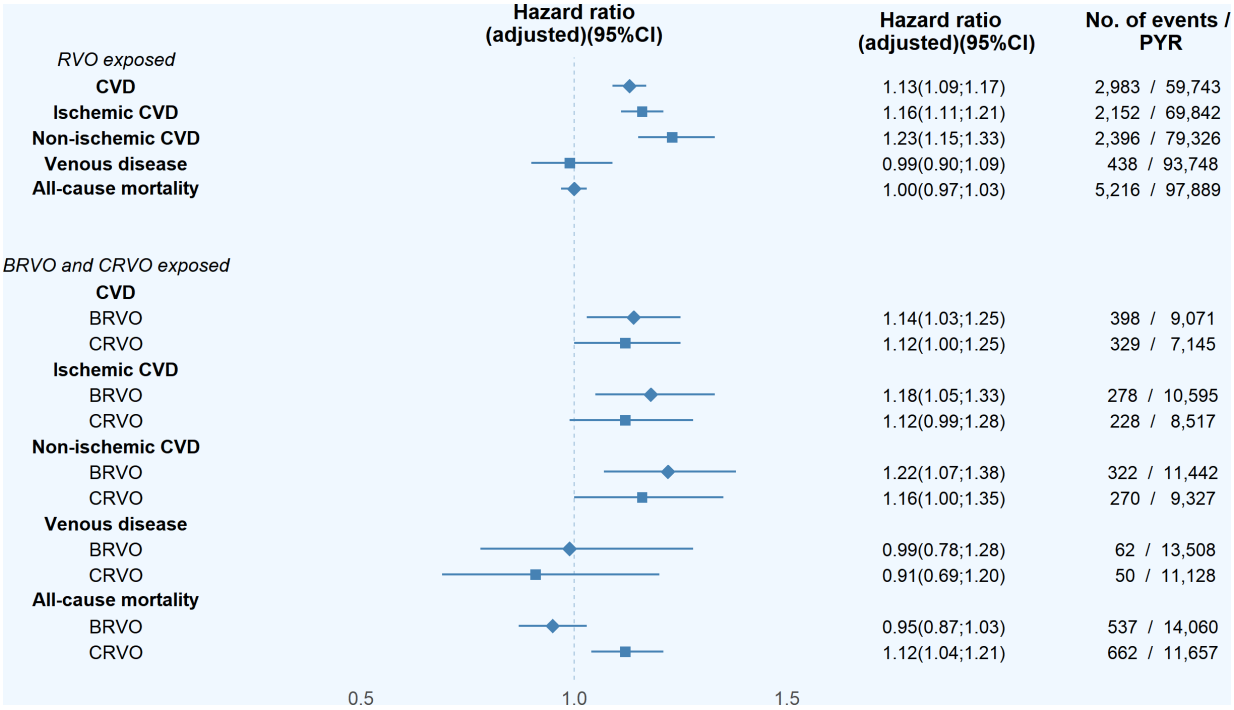

Figure 2 Hazard ratios and no. of events and person-years at risk of CVDs and all-cause mortality in patients with RVO, BRVO and CRVO compared to individuals without RVO. RVO, retinal vein occlusion, BRVO, branch retinal vein occlusion, CRVO, central retinal vein occlusion, CVD, cardiovascular diseases, PYR, person-years at risk.

to 1.35, respectively). We found no association between either BRVO or CRVO and the risk of other venous diseases (adjusted HRs 0.99, 95% CI 0.78 to 1.28, and 0.91, 95% CI 0.69 to 1.20, respectively). In patients with CRVO, we found an increased risk of all-cause mortality (adjusted HR 1.12, 95% CI 1.04 to 1.21), which was not found in BRVO (adjusted HR 0.95, 95% CI 0.87 to 1.03).

Table 2 Baseline characteristics of BRVO and CRVO exposed

	BRVO exposed (n=3683)	CRVO exposed (n=2846)
Sex		
Men	1763 (47.9)	1534 (53.9)
Women	1920 (52.1)	1312 (46.1)
Age at index date (years)	54.0 (45.8–61.8)	56.9 (48.0–64.3)
Age at RVO diagnosis (years)	71.1 (62.6–78.4)	73.0 (64.1–80.5)
No of incident RVO diagnoses, mean no. per year		
1998–2010	32	41
2011–2018	409	289
Charlson Comorbidity Index score		
0 (low)	3421 (92.9)	2614 (91.8)
1	134 (3.6)	108 (3.8)
2	108 (2.9)	103 (3.6)
>3 (high)	20 (0.5)	21 (0.7)
Comorbid conditions		
Arterial hypertension	2438 (66.2)	1867 (65.6)
Dyslipidaemia	1980 (53.8)	1476 (51.9)
Diabetes	636 (17.3)	500 (17.6)
Smoking-related disorders	280 (7.6)	271 (9.5)

Data presented as median (25%–75% percentile) for continuous variables and count (%) for categorical variables.
BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

Evaluation of associations before and after 2011

RVO exposure both prior to and after 2011 (figure 3 and online supplemental table 3) was associated with CVD, ischaemic CVD and non-ischaemic CVD. However, risks increased after 2011, especially for CVD (adjusted HRs 1.10, 95% CI 1.06 to 1.15 vs 1.19, 95% CI 1.11 to 1.28, respectively) and non-ischaemic CVD (adjusted HRs 1.06, 95% CI 1.01 to 1.12 vs 1.24, 95% CI 1.15 to 1.33, respectively). There was no increased risk of all-cause mortality in persons with RVO referred after 2011 (adjusted HRs before 2011: 1.01, 95% CI 0.98 to 1.04 vs after 2011: 0.97, 95% CI 0.91 to 1.02). We found no associations between RVO and venous diseases at any time.

In secondary analysis of patients with RVO stratified by VEGF inhibitory treatment, we found that 523 of 7281 (7.2%) referred to the hospital prior to 2011 received at least one VEGF inhibitory treatment prior to end of follow-up, as opposed to 4146 of 8384 (49.5%) referred after 2011. The VEGF-inhibitory-treated patients referred after 2011 had a more pronounced association with CVD compared with untreated patients (adjusted HRs 1.24, 95% CI 1.12 to 1.37 vs 1.15, 95% CI 1.05 to 1.27, respectively). On the contrary, in patients with RVO referred after 2011, treated patients had lower all-cause mortality than those not treated (adjusted HRs 0.82, 95% CI 0.75 to 0.90 vs 1.09, 95% CI 1.01 to 1.17).

After 2011, BRVO was associated with increased risk of CVD, ischaemic CVD and non-ischaemic CVD (adjusted HRs 1.15, 95% CI 1.02 to 1.29; 1.18, 95% CI 1.02 to 1.35; and 1.22, 95% CI 1.07 to 1.38, respectively; figure 3 and online supplemental table 3), which were not apparent prior to 2011. CRVO and not BRVO exposure were associated with increased all-cause mortality prior to 2011 (adjusted HRs 1.41, 95% CI 1.25 to 1.58, and 0.96, 95% CI 0.82 to 1.13, respectively), but after 2011 neither CRVO nor BRVO exposure associated with increased risk of all-cause mortality (adjusted HRs 0.97, 95% CI

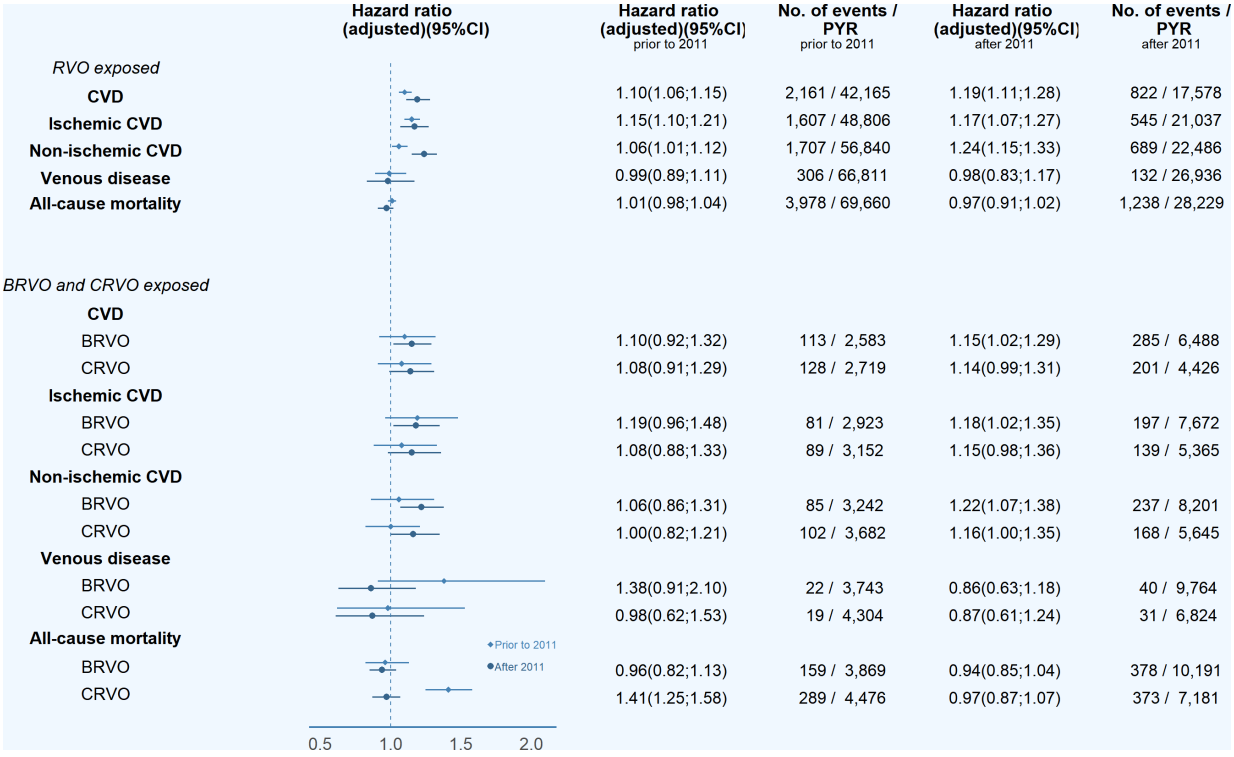

Figure 3 Hazard ratios and no. of events and person-years at risk for CVDs and all-cause mortality in patients with RVO, BRVO and CRVO compared to individuals without RVO prior to and after March 17th 2011. RVO, retinal vein occlusion, BRVO, branch retinal vein occlusion, CRVO, central retinal vein occlusion, CVD, cardiovascular diseases, PYR, person-years at risk.

0.87 to 1.07 and 0.94, 95% CI 0.85 to 1.04, respectively). Evaluated in subgroups of RVO exposed from 2011 to 2014 and from 2015 to 2018 all increases in HRs were most pronounced in patients with RVO diagnosed from 2015 to 2018 (data not shown).

The rates of CVD and mortality outcomes as well as number of events, median time to event and median age at event for exposure groups and unexposed, where applicable, are reported in online supplemental table 4. These data are not directly comparable between groups due to the unmatched design of the study and the time-varying exposure used. In the overall RVO exposure group, a total of 2983 CVD events were recorded, corresponding to a rate of 49.9 per 1000 person-years at risk. Median time to CVD was 3.7 years and median age at CVD diagnosis was 77.3 years.

DISCUSSION

In this 20-year nationwide cohort study, patients with RVO had 13%–23% higher risks to develop overall, ischaemic and non-ischaemic CVD as compared with non-exposed controls and risks increased after 2011. While overall all-cause mortality was not increased, risks were 12% higher in those with CRVO.

To the best of our knowledge, this is the first study evaluating the associations of RVO exposure on CVD and all-cause mortality in a large population-based cohort, including the most recent data on patients after introduction of anti-VEGF for RVO in Europe.

Evaluation of associations between RVO and CVD and all-cause mortality

Previous studies evaluated RVO as an overall exposure for CVD and found associations with ischaemic CVD,[19–23] but not non-ischaemic CVD.[23 24] This agrees with our findings of increased risk of ischaemic CVD, but we reported an increased risk of non-ischaemic CVD in RVO-exposed patients. This difference might be attributed to our design, with non-ischaemic CVD as a pooled outcome of several diagnoses, and perhaps to the amount of patients with RVO in our study being 10-fold that of the comparative studies, increasing the power to detect weaker associations.

Previous studies found no increased mortality in patients with RVO[4 21 25 26] except for a study of Danish patients with CRVO reporting increased mortality risk,[5] in line with our findings in the overall analysis and on RVO exposure prior to 2011.

Evaluation of associations between BRVO and CRVO subgroups on CVD and all-cause mortality

In patients with BRVO and CRVO (figure 2), we found almost similar results in CVD outcomes, though with a tendency to higher risks in patients with BRVO. We found increased risk of all-cause mortality in patients with CRVO that was not found in the BRVO group. Only few previous studies evaluated BRVO and CRVO subgroups separately. Increased risk of incident acute myocardial infarction in patients with RVO, with higher risk in patients with CRVO than BRVO have been reported in a Taiwanese population.[27] Examining data prior to 2010 in Denmark revealed increased risk of congestive heart failure and ischaemic CVD 10 years after BRVO and CRVO.[4 5] This resemble our findings of ischaemic and non-ischaemic disease, but contrary to our study they also reported an increased risk of peripheral vein disease after CRVO.[5]

Evaluation of associations before and after 2011

We found higher risk of CVD overall and non-ischaemic CVD after 2011 and similar risks of ischaemic CVD and venous diseases when comparing patients with RVO referred prior to

and after introduction of VEGF inhibitory treatment for RVO in Europe (figure 3). We found no increased risk of all-cause mortality in the overall RVO group prior to or after 2011.

After 2011, the mean number of registered patients in the DNPR almost doubled (online supplemental figure 1). This reflects a group of patients with RVO who were not treated in hospitals prior to 2011 and, hence, have not been included in prior studies. These patients might have higher risk of CVD than the patients before 2011. If any detection bias of CVD is present, this may also play a role.

Another potential factor is the intravitreal treatment itself. VEGF inhibitors delivered intravitreally are reported to have systemic VEGF-suppressing effects.[28] Meta-analyses of studies on VEGF exposure in patients with diabetic macular oedema and age-related macular degeneration have reported increased risks of CVD with increasing levels of VEGF.[29 30] While safety of intravitreal VEGF inhibition has been established in large clinical trials of RVO[2 3 31–33] and a recent meta-analysis,[34] long-term, real-world data are important, as patients in clinical trials tend to be more healthy than non-study populations. In secondary analysis of patients with RVO referred after 2011, we found that patients with anti-VEGF treatment had slightly higher risk of all CVD but lower risk of all-cause mortality than patients never treated with anti-VEGF. This implies that anti-VEGF might be an intermediary factor in the association between RVO and CVD, but changes in CVD persist when only examining patients with RVO not treated with anti-VEGF.

It is noteworthy that mortality risk after 2011 is unchanged in BRVO, but lower in CRVO. This empowers the interpretation that difference in mortality prior to and after 2011 was a result of changed referral practice and possibly difference in severity of comorbid conditions in patients, rather than the treatment itself, since both subgroups of RVO have been treated with anti-VEGF. It does, however, raise awareness of the fact that patients with CRVO might be in lower risk of mortality than hitherto presumed. It must be taken into consideration that the extent of anti-VEGF treatment in this patient group has a well-established effect on visual acuity outcomes affecting quality of life, underlining importance of receiving the treatment. Our study was not intended or designed to evaluate the direct influence of anti-VEGF treatment on outcomes, and further studies are warranted to quantify this possible relation.

Our study is strengthened by being a long-term, population-based cohort study using validated registries and recent data. It does, however, impose several limitations: First, we have ascertained RVO and CVD in the age group of 40 years and older and those attending hospital eye services and results might not apply outside this setting. Second, lifestyle, socioeconomic and genetic factors are not included in the registers and cannot be evaluated.

In conclusion, patients with RVO had an increased risk to develop overall, ischaemic and non-ischaemic CVD, but not venous disease, compared with non-RVO controls. No overall excess risk of mortality was found, and an increased mortality in CRVO patients prior to 2011 was no longer present after 2011. The risk of CVD, especially non-ischaemic, was markedly higher in patients diagnosed after the change in referral practice for hospitals, when intravitreal angiostatic treatment was introduced. Studies are warranted, designed to further evaluate the potential causes for this difference.

Correction notice Corrections have been made to this article after publication with respect to the results of the all-cause mortality outcome in both overall and subgroup analyses. The text and figures in both article and supplementary material have been adjusted accordingly.

Contributors JG initiated the study. KHF and LS had full access to all data in the study and take responsibility for the data integrity and accuracy of the data analysis. KHF drafted the manuscript. All authors contributed to the design of the study, interpretation of data and critical revision of the manuscript. KHF is the guarantor.

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Data availability statement Data may be obtained from a third party and are not publicly available. Due to general data protection regulation, the raw data cannot be made accessible from the authors. Programming code can be retrieved from the authors on reasonable request.

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