EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2020
EMA/263748/2022

Incidence of Central Retinal Artery Occlusion in the neovascular Age-related Macular degeneration Population

EMA report

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Date	31 May 2020

Background	
Title of query	Incidence of Central Retinal Artery Occlusion in the neovascular age-related macular degeneration population
Associated regulatory procedure	PSUSA

Acknowledgement

IQVIA Medical Research Data (IMRD) incorporates data from THIN, A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care. In order to prevent identification of individuals, numbers of patients from 1-5 have been redacted.

Lay Summary

There is a concern that the eye condition central Retinal Artery Occlusion (cRAO) might rarely be associated with use of the drug aflibercept when it is injected into the eye for the treatment of a different eye condition: neovascular age-related macular degeneration (nAMD). This is being evaluated by the European Union's Pharmacovigilance Risk Assessment Committee (PRAC), a regulatory body responsible for assessing and monitoring the safety of human medicines.

This analysis uses existing data sources to provide estimates of how often cRAO occurs in a population similar to that receiving aflibercept for nAMD. By doing this it allows regulators to assess whether the low number of cases of cRAO in patients treated with aflibercept is in line with expectation. The results of this study will be used by the PRAC in its decision-making process by helping to decide if regulatory action needs to be taken to protect patients receiving aflibercept for nAMD in the future.

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1. Rationale and background

There has been persistent concern over increased risk of central Retinal Artery Occlusion (cRAO) following exposure to intravitreal aflibercept (Eylea®), for which neovascular (wet) age-related macular degeneration (nAMD) is the principal indication. There is a paucity of published data describing the incidence of cRAO in the general population. One US publication described the incidence of cRAO in Olmsted County, Minnesota from 1976 to 2005, but the description of the methods and findings are unhelpful with no breakdown of the event rates by age or sex, and the standardised incidence rates calculated used an unclear reference population (the 2000 census "U.S. white population")[1]. This means it isn't practically possible to apply these data to the nAMD population. A more recent publication derived from German claims data has presented up-to-date stratified incidence rates and overall incidence and prevalence figures standardised to the European Reference population[2]. In this case the study has been published as a Research Letter and some details of the methodology and findings are lacking, although there is a breakdown of event rates by age.

Factors known to be associated with onset of nAMD are age (by far the strongest predictor), sex (females being at greater risk) and smoking history (with smoking being associated with greater risk). Although ethnicity is associated with AMD in general (with European populations being at greater risk), this is not thought to be true for neovascular AMD[3]. Inconsistent findings in various epidemiological studies means that other factors potentially associated with nAMD such as exposure to sunlight, iris colour, alcohol consumption, hypertension and hyperlipidaemia, are not considered established risk factors.

A request was made for additional data on the incidence of cRAO data in the nAMD population using in-house data sources held at EMA (IMRD-France, IMRD-Germany, IMRD-United Kingdom). Pilot data in IMRD-UK (formally THIN) found only a very low level of usage of intravitreal aflibercept: this was unsurprising given it is intended for specialist (secondary care) use only and IMRD-UK records primary care drug exposures. However, it was thought there could be sufficient data to provide estimates of cRAO incidence in a population with the same demographic profile as the nAMD population. Also, in IMRD-Germany and IMRD-France, there was too limited data to study patients with a prescription for aflibercept. In IMRD-Germany and IMRD-France a distinction can also not be made between wet and dry age-related macular degeneration because both diagnoses are coded using the same WHO ICD10 code. Nevertheless, available data on RAO in the overall GP population and in patients with AMD will be provided.

2. Research question and objectives

2.1. IMRD-UK

1. To establish the incidence of cRAO recorded in the general (IMRD-UK) population stratified by age, sex and smoking status.
2. To compare the incidence of cRAO rate between IMRD-UK, AOK Baden-Württemberg and Olmsted County, Minnesota, USA.
3. To describe the demographic makeup of the nAMD population in IMRD-UK in terms of age, sex and smoking status.

[1] Leavitt JA, Larson TA, Hodge DO, Gullerud RE. The incidence of central retinal artery occlusion in Olmsted County, Minnesota. Ophthalmology 2016;123:1999-2003
[2] Pick J, Nickels S, Saalmann F, Finger RP, Schuster AK. Incidence of retinal artery occlusion in Germany. Acta Ophthalmol 2020: doi: 10.1111/aos.14369 [Epub ahead of print]
[3] Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet 2018;392:1147-1159.

4. To derive an estimate of the incidence of cRAO (and other RAO) standardised to the nAMD population (stratified by both age & sex AND age, sex & smoking status).
5. To describe the actual incidence of cRAO (and other RAO) in the nAMD population (accepting that numbers will be very low with the underlying condition and outcome of interest being relatively rare).

2.2. IMRD-Germany and IMD-France

1. To compare the prevalence of cRAO and other RAO (oRAO) in the general population with data from AOK Baden-Württemberg and to provide data on the prevalence of cRAO and oRAO by age and gender.
2. To describe the actual incidence of cRAO (and any RAO) in the AMD population.

3. Research Methods

3.1. IMRD-UK

This analysis used data from IMRD-UK (formerly known as THIN) which originates from the computer systems of General Practitioners (GPs) across the United Kingdom. The data covers about 6% of the UK population and is broadly generalizable to the whole UK. Data on diagnoses and prescribing come from the GP system and are recorded as Read codes and Gemscript codes. The September 2019 version of IMRD-UK contains data from over 790 practices with a total of 17 million patients of which just under 3 million patients are "current".

The population was defined according to the first availability on the database for follow up (the latest of the subjects' date of registration with the GP practice, date of birth, date of Acceptable Mortality Reporting or date of practice computerisation) until the end of follow up (the earliest of transfer out date, date of death or date of last data collection. This was counted on a yearly basis from 2000 until 2018 (the most recent complete year of follow-up).

Three outcome definitions were used: a narrow definition of cRAO only (Read code: F423100, "Central retinal artery occlusion"), other RAO (oRAO) incorporating closely related diagnoses (Read codes: F423200 "Retinal arterial branch occlusion"; F423211 "Branch RAO"; F423500 "Retinal partial arterial occlusion NOS"; and FyuF500 "Other retinal artery occlusions") and a broader definition of *any* RAO incorporating both of these. This follows the approach used by Pick et al where transient forms of RAO were not included[2]. Incident cases were defined as a new-onset cases of RAO in patients with at least one-year of look back in the database and no history of the outcome. Smoking status (classified as "current smoker", "ex-smoker", "never smoker") is regularly recorded for many patients in IMRD-UK. For this analysis the most recently dated smoking record prior to nAMD diagnosis for the "at risk" population or year midpoint for the wider general population was used: where this was not complete (for just 0.69% of the nAMD population) the next subsequent smoking status was used (0.51%), with there being no record for a tiny minority of nAMD patients (0.18%).

Incidence rate was calculated as the number of incident cases of RAO divided by the total population follow up time and is described as the event rate per 100,000 person years (PY). This was stratified by age (using categories as defined by the 1976 European reference population[4] used by Pick et al[2]), sex and smoking status. To allow comparison with previous incidence studies, incidence rates were applied to the 1976 European reference population. To establish the expected event rate in the nAMD population the general population, event rates were applied to the nAMD population stratified by age & sex, and

[4] EUROSTAT Methodologies and Working Papers. 2013 edition.

age, sex & smoking status. To do this, the number of patients with nAMD were stratified by the age (using the same age categories mentioned above), gender and (where applicable) smoking status; and the population event rates were then applied to the nAMD population profile. Confidence intervals for all standardised incidence rates were calculated using the approach of Rothman et al[5].

For incidence of actual events in the population at risk, the same definition was used (Read code: F425200 'Wet senile macular degeneration') including only incident cases of newly diagnosed nAMD in patients without a record of intravitreal aflibercept or other intravitreal injections. The cRAO and oRAO outcomes and stratification variable (age at diagnosis, sex and smoking status) were classified as described above. An analysis was also run using a population of patients with any AMD diagnosis (Read codes: F425.11 'Senile macular degeneration'; F425000 'Unspecified senile macular degeneration'; F425100 'Dry senile macular degeneration'; F425200 'Wet senile macular degeneration').

3.2. IMRD-Germany and IMD-France

The IMRD-Germany database contains anonymised electronic medical record data from a representative panel of physicians since 1992 (GPs and specialists). The sampling of participating physicians is stratified for specialist groups, regions, and age of the physician. IMRD-Germany contains patient records including diagnoses, prescriptions, referrals, hospitalisations and sick notes. The sampling of physicians ensures that patients are representative for each speciality across regions in Germany with 83% of practices being single physician practices. As registration with a GP is not a requirement in Germany, patients with a consultation during the time period will be used as denominator in prevalence calculations. The GP patient population is broadly representative of the German population in terms of gender and age distribution, except for children as parents may choose to visit a paediatrician directly.

IMRD-France (formerly known as IMS Disease Analyzer France) contains data from a sample of around 2% of all general practitioners (GPs) across France. The data has been collected since 1997. In France, patients have free physician choice and it is not mandatory to record a diagnosis.

Both IMRD-Germany and IMRD-France diagnoses are ICD10 coded, and prescribed medicines are coded as active substance and EphMRA ATC code. The June 2019 version of IMRD-Germany and IMRD-France were used in this study. In IMRD-Germany the analysis was restricted to the GP (non-specialist) population, where 73% of the RAO diagnosis was recorded.

The prevalence of cRAO, oRAO and any RAO was calculated on a yearly basis (from 2007 to 2018) as the number of patients with a RAO diagnosis divided by the number of patients with at least one event recorded in the database during the given year. This was then stratified by age and sex and expressed as a prevalence per 100,000 patients standardised to the 1976 European reference population. A pooled prevalence was calculated separately for cRAO, oRAO and any RAO by adding all patients with a case across years 2007-2018 divided by the total number of patients, stratified by age and sex and expressed per 100,000 patients. The total number of patients for the pooled denominator was calculated by adding-up the total number of patients of each individual year. Patients were excluded from the population included in the prevalence calculation when age or sex were not recorded (0.03% of patients with a RAO diagnosis in IMRD Germany had no age or birthdate recorded).The cRAO and oRAO events were identified based on the ICD-10 codes (H34.1 for cRAO and H34.2 for oRAO).

Patients with a diagnosis of AMD were identified based on the ICD 10 code H35.3. AMD patients were considered incident if they had at least 365 days of observation prior to the first AMD diagnosis with no prior record of cRAO up to the date of the first AMD diagnosis. No prior record of oRAO was also required

[5] Greenland S, Rothman, KJ. Introduction to Stratified Analysis. In Modern Epidemiology, Third Edition. Philadelphia, PA : Wolters Kluwer/Lippincott Williams & Wilkins Health, 2008

in incident patients that were followed up for both cRAO and oRAO. The incidence rate was calculated as the incident number of cases per 100,000 person-years of follow-up.

4. Results

4.1. IMRD-UK

4.1.1. Population incidence analyses

In the general population there were 1,794 incident cases of cRAO in 85,191,347 patient years of follow-up, 2,011 incident cases of other RAO in 85,191,229 patient years of follow-up and 3,726 incident cases of any RAO in 85,190,413 patient years of follow-up. The distribution of incidence rate by age for all RAO (cRAO and oRAO combined) is shown in Figure 1 and the distribution by age and sex shown in Figure 2. The European age-standardised incidence rate was 1.38 (95% CI 1.32-1.45) per 100,000 PY for cRAO and 1.62 (95% CI 1.55-1.70) per 100,000 PY for oRAO.

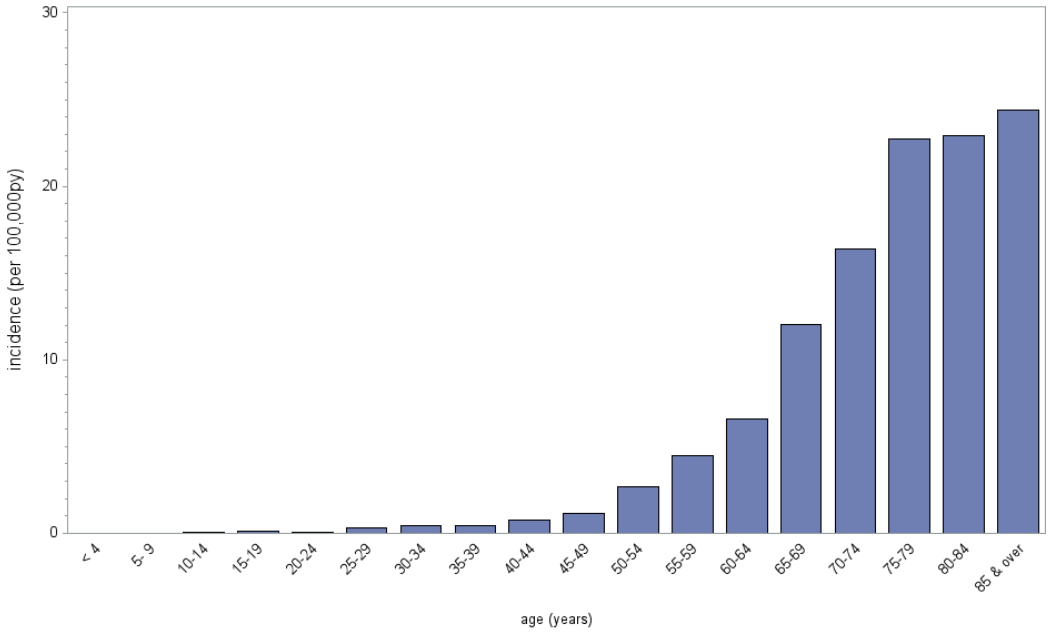

Figure 1. Incidence rate of all retinal artery occlusion in IMRD-UK stratified by age from 2000-2018

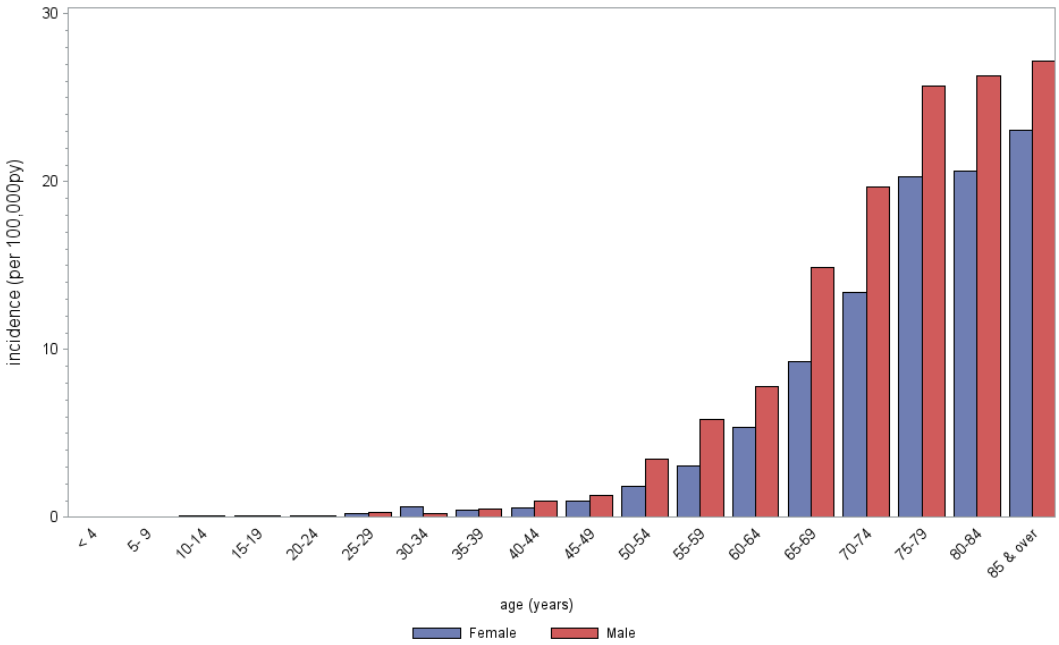

Figure 2. Incidence rate of all retinal artery occlusion in IMRD-UK stratified by age and sex from 2000-2018

4.1.2. Expected incidence in nAMD population analyses

In IMRD-UK there were 8,443 incident cases of nAMD, with 5,350 (63.4%) being female. The mean age at diagnosis was 79.6 years (median 80.0, minimum 26, maximum 103 years). Smoking status was classified as current smokers (11.5%), ex-smokers (49.4%), never smokers (38.9%) and unknown (0.18%).

The RAO incident event rate standardised to the nAMD population is shown in Table 1 and varied between 10.8 and 21.9 depending on the definition and standardisation used.

Table 1. Event rates standardised by age & sex applied to the neovascular AMD population

Outcome	**Standardised rate (per 100,000 py)**	
	Age-sex	Age, sex & smoking
Central RAO	10.8 (10.1-11.5)	11.4 (10.7-12.1)
Other RAO	10.2 (9.60-10.9)	10.9 (10.2-11.6)

4.1.3. Observed incidence rate in nAMD population

Amongst 8,027 nAMD patients, there were <5 incident cases of cRAO (crude incidence rate 10.2 per 100,000 PY (95% CI X.XX-XX.XX). For other RAO there were 6 events in 29,478 PY of follow-up (a rate of 20.4 95% CI 7.47-44.3). A broadly similar pattern was seen for the much larger population of patients with any AMD diagnosis (including "dry" and "non-specific" AMD). Of note, in these analyses, incident cases of RAO tended to occur closer to the time of diagnosis and the risk of both cRAO and any RAO decreased with time. For the nAMD population, the less than 5 cRAO events all occurred within the first

year of follow-up and none thereafter: the crude event rate dropped from 40.8 per 100,000 PY (95% CI X.XX-XXX.X) in the first year of follow-up, to 10.2 per 100,000 PY (95% CI X.XX-XX.X) at the end of all follow-up time. The same was seen for oRAO in nAMD with the event rate dropping from 40.8 per 100,000 PY (95% X.XX-XXX.X; n_{events} = <5) in the first year to 20.4 per 100,000 PY (95% 7.47-44.30; n_{events} = 6) by the end of follow-up.

4.2. IMRD-Germany and IMD-France

4.2.1. Population prevalence analyses

In the GP population in Germany there were 2,174 patients with any RAO in a population of 9,440,843 unique patients across years 2007-2018. A total number of 67,921 patients were excluded from the analysis due to missing age or sex information. Across years 2007-2018 the pooled total number of patient-years of experience (estimated as the sum of the yearly number of patients between 2007 and 2018) was 28,934,088 and cRAO was diagnosed in 1,085 patients, oRAO in 2,174 and any RAO in 3,229. The pooled prevalence of cRAO and any oRAO by age and sex is shown in Figure 3. The European age-standardised prevalence per year for cRAO, and oRAO and any RAO are shown in Figure 4. The pooled European age-standardised prevalence across years 2007-2018 was 1.86 per 100,000 patients for cRAO, 3.94 per 100,000 patients for oRAO and 5.74 per 100,000 patients for any RAO.

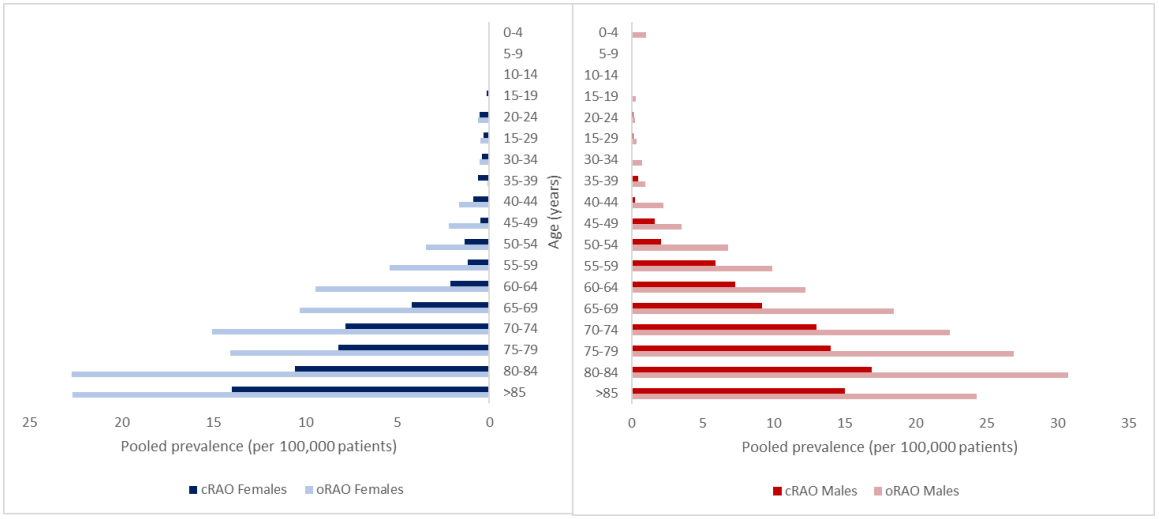

Figure 3. Pooled prevalence of central retinal artery occlusion (cRAO) and other retinal artery occlusion (oRAO) in IMRD-Germany stratified by age and sex for the period 2007-2018

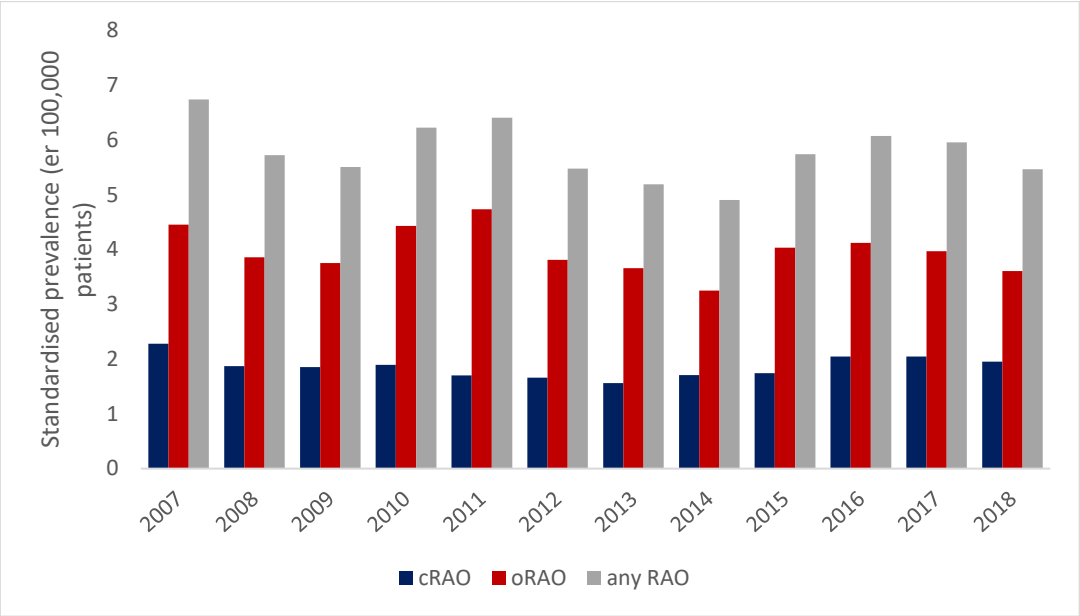

Figure 4. European age-standardised prevalence of central retinal artery occlusion (cRAO), other retinal artery occlusion (oRAO) and any retinal artery occlusion (any RAO) in IMRD-Germany for years 2007-2018

In the GP population in France there were 196 patients with any RAO in a population of unique 3,230,849 patients across years 2007-2018. A total number of 10,857 patients were excluded from the analysis due to missing information on age or sex. Across years 2007-2018 the pooled total number of patient-years of experience (estimated as the sum of the yearly number of patients between 2007 and 2018) was 9,384,838 and cRAO was diagnosed in 49 patients, oRAO in 199 and any RAO in 247. The pooled prevalence of cRAO and oRAO by age and sex is shown in Figure 5. The European age-standardised prevalence per year for cRAO, oRAO and any RAO are shown in Figure 6. The pooled European age-standardised prevalence across years 2007-2018 was 0.38 per 100,000 patients for cRAO, 1.65 per 100,000 patients for oRAO and 2.01 per 100,000 patients for any RAO.

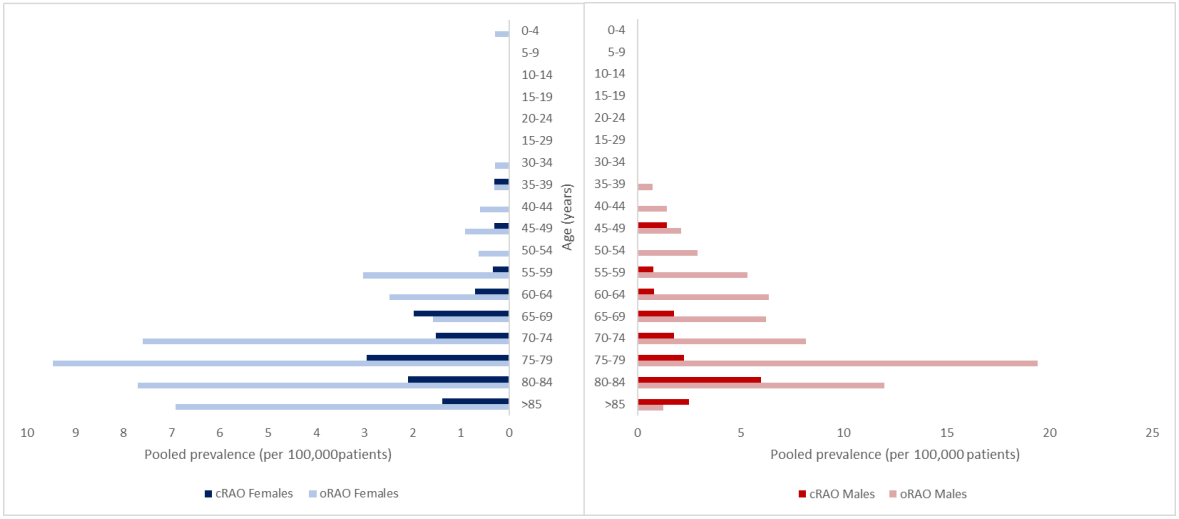

Figure 5. Pooled prevalence of central retinal artery occlusion (cRAO) and other retinal artery occlusion (oRAO) in IMRD-France stratified by age and sex for the period 2007-2018

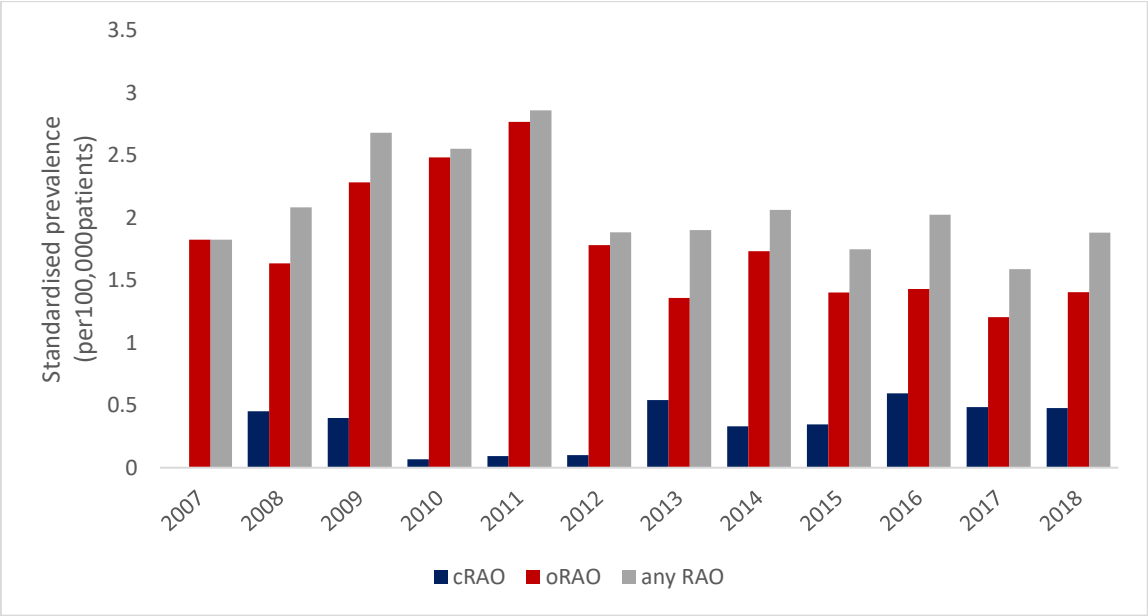

Figure 6. European age-standardised prevalence of central retinal artery occlusion (cRAO), other retinal artery occlusion (oRAO) and any retinal artery occlusion (any RAO) in IMRD-France for years 2007-2018

A comparison of the incidence and prevalence figures for Olmsted County, Minnesota, USA; Baden-Württemberg, Germany; IMRD-DE; IMRD-FR and IMRD-UK is shown in Table 2 at the end of this report.

4.2.2. Incidence rate in patients with age-related macular degeneration

In IMRD-Germany amongst 14,935 AMD patients with 64,766 PY of follow-up there were 8 incident cases of cRAO (rate 12.4 per 100,000 PY; 95% CI 5.3-24.3). For any RAO there were 30 events in 64,425 PY of follow-up (a rate of 46.6 per 100,000 PY; 95% CI 31.4-66.5). The distribution of incident cRAO after the AMD diagnosis was the following: 0-3 months (0 cases), 4-6 months (1 case), 7-12 months (1 case), 13-24 months (0 cases), 25-36 months (2 cases), 36-48 months (1 case), ≥ 5 years (3 cases).

In IMRD-France amongst 1,122 AMD patients with 3,856 PY of follow-up there were no incident cases of cRAO. For any RAO there was a rate of 26.0 per 100,000 PY; 95% CI 0.7-145.1).

In IMRD-Germany and IMRD-France, 65% of patients diagnosed with AMD were female and 35% were male. The mean (median) age in IMRD-Germany was 75.8 (78.0) years (min 2, max 98). In IMRD-France the mean (median) age was 77.8 (79.0) years (min 4, max 102). Please note that in IMRD-Germany age is not recorded above 99 years. In IMRD Germany, smoking information was recorded in only around 10% of AMD patients and was therefore not considered.

5. Discussion

The incidence and prevalent rates for cRAO in the three IMRD databases on which this analysis is based are lower than that recently published for AKO Baden-Württemberg. The incidence rate in the IMRD-UK population is approximately half that observed in the AKO Baden-Württemberg population, although the shape of the age distributions was similar for both (Figure 1). The prevalence data for IMRD-DE is about a third of that for AKO Baden-Württemberg and IMRD-FR is lower still. This is despite the AKO Baden-Württemberg study having an apparently more stringent case definition (a RAO code in one quarter of the year confirmed in one of the following three quarters or coded at least once as inpatient). It is not entirely clear what differentiated an incident from a prevalent case in the AKO Baden-Württemberg study, and this could have led to the difference. Comparison with the US data is difficult because of the poor

presentation of the US data: broadly the findings are similar to IMRD data sources which all also found a higher incidence / prevalence rates for males (Figures 2 and 3), although perhaps less pronounced. The distribution between genders was not described for the AKO Baden-Württemberg data.

Likely explanations for the lower standardised event rates between the IMRD and AKO Baden-Württemberg data are:

- an overestimate of the population denominator in IMRD-UK data. This could occur in the UK data because registration data might not be fully up to date and accurate – an alternative for the UK data would be to only use patients "actively" using the healthcare system; however, this would be likely to underestimate the population denominator and this approach isn't commonly used for UK primary care data sources. This could not explain the findings in IMRD-Germany and IMRD-France, where the population denominator is calculated from patients actively seeking healthcare, which underestimates the true population denominator.
- an underestimate of the incident / prevalent case numerators in the IMRD data, because of incomplete recording of a specialist diagnosis: the seriousness of the condition means that accurate and up-to-date recording of the diagnosis would be expected; however, it is possible that it might be missing for especially complex patients with multiple comorbidities. Moreover, in France it is not mandatory for the GP to record a diagnosis, and there appears to be under-recording of RAO in the French IMRD data.
- a potentially skewed population denominator in the AKO Baden-Württemberg. This was based on "all insured patients" and may not be reflective of the true population at risk: the description of how the population denominator was derived is limited.
- an overestimate of the incident / prevalent cases numerator in the AKO Baden-Württemberg data. This would imply better or over-recording of events compared to the other databases; however, as mentioned above, this seems unlikely given the more stringent case definition used.
- a true difference in risk between the underlying populations: this would be a novel finding and seems unlikely given the two of the data sources are derived from the same country.

The observation that the risk of cRAO and any RAO decreases with time following initial diagnosis of nAMD within IMRD-UK could be significant. It is possible that this is cause by an ascertainment bias such that the outcome (RAO) is more readily diagnosed in those who are having their macular degeneration monitored (or vice versa). The same phenomenon wasn't observed for the IMRD-DE data and could be a nuance relating to UK primary care data.

The strengths of this study are that the data arise from complete, representative and well-defined population bases. Given the severity of the conditions, there is a high likelihood of accurate recording of both RAO and AMD in primary care. Broadly, there is consistency of finding between the various databases. Weaknesses are lack of data describing the validity of the codes used to identify AMD and RAO for all data sources, the relatively low numbers of patients with an outcome (RAO being a very rare condition), lack of differentiation between "wet" and "dry" forms of AMD for most data, and the risk that diagnosis of AMD being made at around the same time as RAO (as an incidental finding), but without the temporal relationship of the two being clear. The extent of these issues varies by data source.

6. Conclusion

In summary, published and unpublished analyses suggest the incidence of cRAO in the nAMD population to be in the region of 10 - 20 cases per 100,000 PY, with the *observed* cRAO event rate in nAMD patients being comparable to the *expected* event rate derived by applying the general population event rate to the nAMD population demographic. There is, however, some variation between data sources.

7. References

1. Leavitt JA, Larson TA, Hodge DO, Gullerud RE. The incidence of central retinal artery occlusion in Olmsted County, Minnesota. Ophthalmology 2016;123:1999-2003

2. Pick J, Nickels S, Saalmann F, Finger RP, Schuster AK. Incidence of retinal artery occlusion in Germany. Acta Ophthalmol 2020: doi: 10.1111/aos.14369 [Epub ahead of print]

3. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet 2018;392:1147-1159

4. EUROSTAT Methodologies and Working Papers. 2013 edition

5. Greenland S, Rothman, KJ. Introduction to Stratified Analysis. In Modern Epidemiology, Third Edition. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health, 2008

Table 2. Comparison of Retinal Artery Occlusion incidence and prevalence rates from 2 publications and 3 in-house EMA data sources

Study	**Leavitt *et al* 2011** [1]	**Pick *et al* 2020** [2]	**IMRD-DE**	**IMRD-FR**	**IMRD-UK**
Population	Olmsted County, Minnesota, USA 1976-2005	Baden-Württemberg, Germany, 2016	Germany, 2007-2018	France, 2007-2018	UK, 2000-2019
Data source	secondary care case records	AOK claims data	Primary care records?	Primary care records?	Primary care records
Definition(s)	retinal embolism, retinal infarction, Hollenhorst plaque, retinal ischemia, retinal artery occlusion, retinal artery obstruction, artery eye occlusion, retinal vascular occlusion, unspecified retinal ischemia, partial retinal arterial occlusion, retinal arterial branch occlusion and transient retinal arterial occlusion IN COMBINATION WITH clinical history of abrupt vision loss AND fundus findings of retinal opacification or a cherry red spot or both	**cRAO** ICD10: H34.1 'central RAO' **oRAO** ICD10: H34.2: 'other RAO' (including branch RAO, partial RAO, retinal microembolism)	**cRAO** ICD10: H34.1 'central RAO' **oRAO** ICD10: H34.2: 'other RAO' (including branch RAO, partial RAO, retinal microembolism)	**cRAO** ICD10: H34.1 'central RAO' **oRAO** ICD10: H34.2: 'other RAO' (including branch RAO, partial RAO, retinal microembolism)	**cRAO** Read: F423100 'central RAO' **oRAO** Read: F423200 'Retinal arterial branch occlusion' F423211 'Branch RAO' F423500 'Retinal partial arterial occlusion NOS' FyuF500 'Other retinal artery occlusions'
Reference population	"white population" from 2000 USA census	European standard population (1976)	European standard population (1976)	European standard population (1976)	European standard population (1976)
	Standardised incidence / prevalence (per 100,000 PY)				
Central RAO	1.90 / -	2.7 / 6.2	- / 1.86	- / 0.38	1.38 / -
Other RAO	- / -	4.5 / 11.7	- / 3.94	- / 1.65	1.62 / -
Any RAO	- / -	- / -	- / 5.74	- / 2.01	