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VEGF Inhibition Associates With Decreased Risk of Mortality in Patients With Neovascular Age-related Macular Degeneration

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Purpose: Controversy exists regarding the systemic safety of intravitreal VEGF inhibitors in the treatment of neovascular age-related macular degeneration (nAMD). We aimed to investigate the potential impact of VEGF inhibitor treatment on the risk of all-cause mortality and cardiovascular disease (CVD) among patients with nAMD.

Design: A nationwide register-based cohort study with 16 years follow-up.

Participants: Patients with nAMD exposed with VEGF inhibitors (n = 37 733) and unexposed individuals without nAMD (n = 1 897 073) aged ≥ 65 years residing in Denmark between January 1, 2007, and December 31, 2022.

Methods: Cox proportional hazards analysis was conducted to assess the effect of intravitreal VEGF inhibitor treatment on all-cause mortality and incident CVD.

Main Outcome Measures: In a predefined analysis plan we defined primary outcomes as hazard ratios (HRs) of all-cause mortality and a composite CVD endpoint in patients with nAMD treated with VEGF inhibitors compared with individuals without nAMD. The secondary outcomes encompassed analyses that explored the impact of the number of doses and the association between exposure and outcome over a specific time period.

Results: Overall, 63.7% of patients with nAMD were women with an average age of 69.9 years (interquartile range 65.0−76.0 years). Patients exposed to VEGF inhibitors demonstrated a reduced risk of all-cause mortality compared with individuals without nAMD (HR, 0.79; 95% confidence interval [CI], 0.78−0.81), and an increased risk of composite CVD (HR, 1.04; 95% CI, 1.01−1.07). The decreased risk of all-cause mortality persisted, but there was no significant association between VEGF inhibitor treatment and CVD when patients with nAMD were grouped by the number of doses or considered exposed within 60 days postinjection.

Conclusions: Our study revealed a decreased risk of all-cause mortality and a 4% increased risk of CVD among patients with nAMD exposed with VEGF inhibitors. The decreased risk of mortality is unlikely to be directly pathophysiologically related to VEGF inhibitor treatment. Instead, we speculate that patients undergoing VEGF inhibitor treatment are, on average, individuals in good health with adequate personal resources. Therefore, they also have a higher likelihood of overall survival. These findings strongly support the safety of VEGF inhibitor treatment in terms of all-cause mortality and CVD among patients with nAMD.

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Neovascular age-related macular degeneration (nAMD) is a common retinal disease characterized by the abnormal growth of blood vessels beneath the macula, leading to visual impairment.[1,2] The introduction of VEGF inhibitors has revolutionized the therapeutic landscape for nAMD, and has demonstrated remarkable efficacy as a first-line treatment option since the approval in 2006.[3−5] Intravitreal administration of VEGF inhibitors not only exerts a local effect within the eye but also results in systemic VEGF suppression.[6] The systemic exposure to these agents varies depending on the specific drug and treatment regime, with plasma concentrations above the half maximal inhibitory concentration (IC50) measured for up to 90 days postinjection.[7] Studies have even shown systemic accumulation of VEGF inhibitors after consecutive monthly injections.[8] While the impact of systemic VEGF suppression on adverse events is still uncertain, it is essential to carefully consider the potential risks and benefits. Most studies investigating the safety profile of VEGF inhibitors have reported no serious complications associated with treatment.[9−11] However, some studies suggest that certain patient subgroups, such as those with

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diabetic macular edema and other higher-risk individuals, may experience more severe adverse events.[12,13] For instance, high-intensity treatment in diabetic macular edema patients has been associated with an increased risk of mortality and cerebrovascular events.[8] Although clinical trials have demonstrated the safety of VEGF inhibitor agents for various indications, including nAMD, it is important to note that these trials often have relatively short follow-up periods and may be underpowered to evaluate rare events.[14] Therefore, further validation of the safety profile of VEGF inhibitors is warranted, particularly in terms of assessing all-cause mortality and cardiovascular disease (CVD) risks among patients with nAMD. The primary objective of this nationwide study was to investigate whether treatment with intravitreal VEGF inhibitors is associated with an increased risk of all-cause mortality and composite CVD in patients diagnosed with nAMD. Additionally, we aimed to assess the potential impact of number of treatment doses and time-dependent relationship on the observed association.

Methods

Study Design and Data Sources

This population-based cohort study utilized data from Danish national registries. The Danish National Patient Registry offered comprehensive information on hospitalizations since 1977 and outpatient contacts since 1995.[15] Diagnoses were coded using the International Classification of Diseases eighth (1977−1993) and tenth (1994−present) revisions, while procedures were classified according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures.[16] The Civil Registration system contained vital status, migration, marital status, and unique personal registration numbers, enabling efficient linkage across all registries.[17] Data on redeemed prescriptions were obtained from the Danish National Prescription registry, coded according to the Anatomical Therapeutic Chemical Classification System.[18,19]

Study Population

We identified the study population as individuals aged $\geq$ 65 years, residing in Denmark between January 1, 2007, and December 31, 2022.

Exposure

Exposed patients were defined as those with a diagnostic code for nAMD (International Classification of Diseases 10 H353+K+J) and any registered treatment with an intravitreal VEGF inhibitor agent (Nordic Medico-Statistical Committee Classification of Surgical Procedures code KCKD05B "Puncture of the vitreous with injection of angiostatic medicine") during the follow-up period. The date of the first registration of VEGF inhibitor treatment was considered as the initial exposure. We excluded patients from the study if they had received VEGF inhibitor treatment, but did not have a diagnostic code for nAMD.

Outcomes

Primary outcomes included all-cause mortality and a composite CVD endpoint. The composite CVD endpoint encompassed heart failure, acute myocardial infarction, ischemic stroke (including transitory ischemic attack), intracranial hemorrhage, and peripheral arterial disease, as defined by diagnostic codes adapted from Frederiksen et al that modified Hvidberg's definition.[9,20] To increase validity, we included heart failure and peripheral arterial disease diagnoses only when registered as the primary diagnosis, reflecting the main reason for hospitalization.[9] Individuals with a registration of these outcomes before exposure to VEGF inhibitors agents were excluded when analyzing the association with CVD.

Covariates

The selection of covariates was guided by a priori knowledge. The covariates included sex, age at entry, marital status at entry (never married, married/cohabiting, widowed/divorced), arterial hypertension, dyslipidemia, diabetes mellitus, and chronic obstructive pulmonary disease as a proxy for heavy smoking. In addition, we incorporated all the comorbidities from the Charlson Comorbidity Index as individual dichotomous variables in our analysis, excluding diabetes mellitus and chronic obstructive pulmonary disease, as these conditions were defined separately (Table S1).[21] Comorbidities were defined using diagnostic codes, and in relevant cases, the registration of prescription drugs.[9,20]

Analysis

All analyses were conducted in accordance with a preplanned statistical analysis plan, with predefined outcome measures. No changes were made to the analysis plan after the study commenced. Baseline characteristics and demographics were presented as medians and quartiles (25% and 75%) and counts and proportions as appropriate. Charlson Comorbidity Index scores were calculated at study entry and presented in categories for descriptive purposes. We utilized a multivariate Cox proportional hazards model to compare all-cause mortality and risk of CVD between exposed and individuals not exposed. Crude, semiadjusted, and hazard ratios (HRs) were estimated, accompanied by 95% confidence intervals (CIs), along with the number of events and total risk time. The semiadjusted model was adjusted for sex and age at entry, while the fully adjusted model incorporated additional adjustments for marital status at entry and time-varying comorbidities. A time-varying exposure approach was employed, wherein patients with nAMD transitioned from unexposed to exposed at the first record of VEGF inhibitor treatment. The number of days since the 65th birthday served as the underlying time scale. Participants were followed until death, occurrence of CVD events, emigration, or the end of the study period (December 31, 2022), whichever came first. Comorbidity covariates were adjusted for as binary (yes/no) time-varying variables.

The model control of our main analysis uncovered a significant interaction between exposure and age as well as gender. As a result, we conducted separate analyses for women and men and categorized them into different age groups (Tables S2 and S3).

Conducting a sensitivity analysis, patients with diagnostic codes for retinal vein occlusion or diabetic macular edema, along with their diagnostic codes for nAMD, were excluded from the study. This exclusion did not result in statistically significant alterations to the results for either all-cause mortality or CVD. These patients were therefore not excluded (Table S4).

Secondary Outcome Analyses

We conducted 2 additional analyses focusing exclusively on patients with nAMD (n = 37 733), to explore the relationship between exposure to VEGF inhibitor agents and outcomes. First, we examined their exposure to VEGF inhibitor treatment from the day of injection until 60 days postinjection. Following this period, they

were considered unexposed until an eventual subsequent injection which occurred > 60 days after last injection. This analysis aimed to evaluate an association between the exposure to VEGF inhibitor treatment and outcomes within a restricted time period. Second, patients were categorized based on the number of injections received: 1−3, 4−20, 21−40, 41−70, and > 70 injections. We compared the risk of all-cause mortality and CVD with patients who received 1−3 injections of intravitreal VEGF inhibitors as the reference group. We evaluated the association between the number of injections and the occurrence of the outcomes in a Cox regression model. All analyses were carried out using Stata 17.0 (StataCorp LLC).

Ethics

Ethical approval and informed content from participants were not required for this registry-based research conducted in Denmark. The study was assigned the record number 22/10138 in the register of the Region of Southern Denmark and the Danish Health Authorities (FSEID-00004087) to extract and process the data. It is important to note that investigators had access only to the specific study population, which was pseudonymized, along with their relevant information, and not the overall registry population. This approach ensures the confidentiality and privacy of the participants' information. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Results

Baseline Characteristics and Descriptive Statistics

We identified 37 733 individuals with nAMD and 1 897 073 without nAMD > 65 years of age. We found 63.7% of patients with nAMD to be women and on average 69.9 years of age at entry (interquartile range 65.0−76.0 years). There were a higher amount of divorced or widowed individuals among patients with nAMD compared with individuals with no nAMD, yet a high or moderately high comorbidity score according to Charlson Comorbidity Index was less likely among patients with nAMD (Table 5). We observed no significant difference in the prevalence of chronic obstructive pulmonary disease or dyslipidemia between the 2 groups, but patients with nAMD had a lower prevalence of diabetes compared with individuals without nAMD.

The average duration from entry until emigration, end of follow-up, or outcome, whichever came first, was 4.8 years in the analysis of all-cause mortality and 4.5 years in the analysis of CVD for patients with nAMD. Among the patients with nAMD, 10% received injections for > 10.3 years, while 10% received injections for < 1 year.

Primary Outcome

In the fully adjusted model, patients with nAMD demonstrated a reduced risk of all-cause mortality compared with individuals without nAMD (HR, 0.79; 95% CI, 0.78−0.81). When we stratified the analysis by age groups and considered both men and women separately, we observed a significant decrease in the risk of all-cause mortality across all groups (Table S2).

After excluding 8796 patients with nAMD and 485 155 individuals without nAMD due to incident CVD prior to study entry, we found an increased risk of composite CVD in individuals with nAMD (HR, 1.04; 95% CI, 1.01−1.07) (Table 6). We observed no association between exposure to VEGF inhibitor treatment and CVD in any of the age groups, except for both men and women aged 65−70 years in the fully adjusted model (Table S3).

Secondary Outcomes

In our analysis focusing exclusively on patients with nAMD and restricting the time counting as exposed to VEGF inhibitor treatment from the day of injection until 60 days after the injection, after which the follow-up time returned to count as unexposed, we discovered a low HR for all-cause mortality (HR, 0.26; 95% CI, 0.25−0.27) and composite CVD (HR, 0.82; 95% CI, 0.78−0.86) (Table 7).

In the analysis, where patients with nAMD were categorized based on the number of injections compared with patients who received 1−3 injections, we noticed that the HR of all-cause mortality was lower in patients receiving > 20 injections (HR, 0.89; 95% CI, 0.84−0.94), > 40 injections (HR, 0.84; 95% CI, 0.78−0.91) and > 70 injections (HR, 0.78; 95% CI, 0.67−0.91). Additionally, we did not observe a statistically significant association with the risk of composite CVD in any of the categories (Fig 1).

Discussion

In this nationwide register-based cohort study, we aimed to assess the potential risks associated with VEGF inhibitor treatment in patients with nAMD. Our findings generated noteworthy results, with a 20% decreased risk of all-cause mortality and a modest 4% increase in the risk of CVD observed among patients with nAMD. We found a decreased risk of all-cause mortality and composite CVD outcome when analyzing the association between exposure to VEGF inhibitor treatment and outcomes within a restricted time period. When patients were categorized based on the number of injections, no association between VEGF inhibitors and the risk of composite CVD was found. Yet, we revealed a decreased risk of all-cause mortality in patients who received > 20 injections compared with those who received 1−3 injections. Exploring the risk of mortality and CVD in patients receiving intravitreal VEGF inhibitors was motivated by previous studies demonstrating systemic concentrations of these inhibitors and their impact on plasma free-VEGF levels following intravitreal injection.[6,9,12] Although VEGF inhibitors were initially developed for cancer treatment and have known adverse effects on the gastrointestinal and cardiovascular systems, it is crucial to highlight that the systemic concentrations achieved with intravitreal use are substantially lower compared with other therapeutic applications.[22] The decreased risk of all-cause mortality observed in our study has not been reported in previous studies and we do not expect the medication itself to have a protective effect on mortality and development of CVD.[23−25] Considering the physiological

Table 5. Descriptive Characteristics of Patients With and Without nAMD

Characteristics	Individuals Without nAMD (n = 1 897 073)	Patients With nAMD (N = 37 733)	*P* Value
Sex, n (%)			
Women	1 006 462 (53.1)	24 023 (63.7)	< 0.001
Men	890 611 (46.9)	13 710 (36.3)	
Age at entry, years, median (IQR)	65.0 (65.0–72.1)	69.9 (65.0–76.0)	< 0.001
Marital status, n (%)			
Never married	650 934 (34.3)	13 581 (36.0)	< 0.001
Married or living together	1 001 075 (52.8)	17 924 (47.5)	
Divorced or widow	245 064 (12.9)	6228 (16.5)	
Charlson Comorbidity Index score, n (%)			
0 (low)	1 499 140 (79.0)	30 857 (81.8)	< 0.001
1 (moderate low)	138 718 (7.3)	2936 (7.8)	
2 (moderate high)	187 174 (9.9)	3084 (8.2)	
3 (high)	72 041 (3.8)	856 (2.3)	
Diabetes, n (%)			
No	1 721 063 (90.7)	34 617 (91.7)	< 0.001
Yes	176 010 (9.3)	3116 (8.3)	
Dyslipidemia, n (%)			
No	1 381 226 (72.8)	27 469 (72.8)	0.97
Yes	515 847 (27.2)	10 264 (27.2)	
COPD, n (%)			
No	1 818 012 (95.8)	36 188 (95.9)	0.48
Yes	79 061 (4.2)	1545 (4.1)	
Hypertension, n (%)			
No	1 187 408 (62.6)	23 363 (61.9)	0.007
Yes	709 665 (37.4)	14 370 (38.1)	

COPD = chronic obstructive pulmonary disease; IQR = interquartile range; nAMD = neovascular age-related macular degeneration.

implausibility of the observed outcome, we hypothesize the potential presence of confounding by indication, despite adjusting for comorbidities. This speculation arises from the possibility that patients selected for VEGF inhibitor treatment may exhibit lower frailty and less severe comorbidities, factors that may not be adequately captured in registry-based data. Furthermore, there is a statistical indication that the likelihood of survival may increase with a higher cumulative number of injections, potentially due to selection bias. The group of patients receiving multiple injections is a highly selected population consisting of elderly individuals who are healthy enough to visit the hospital frequently, often every fourth week, for an extended period of time. The cumulative number of injections was included as a time-varying variable in order to moderate the impact of immortal time bias, but this might not have removed the full effect of this positive selection. However, if this premise is valid, it raises the question of whether the same applies to the risk of CVD. In such a

Table 6. HRs and 95% CI for All-cause Mortality and Composite CVD in Patients With Neovascular Age-related Macular Degeneration Compared with Individuals Without the Condition

VEGF Inhibitor Exposure	Deaths (n)	Follow-Up (PYR)	Mortality Rate (per 1000 PYR)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Fully Adjusted HR† (95% CI)
All-cause mortality						
Yes	12 870	178 685	72.03	0.79 (0.78; 0.81)	0.84 (0.83; 0.85)	0.79 (0.78; 0.81)
No	709 980	16 387 583	43.32	ref.	ref.	ref.
VEGF Inhibitor Exposure	**Events (n)**	**Follow-Up (PYR)**	**Incidence (per 1000 PYR)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**	**Fully Adjusted HR† (95% CI)**
Composite CVD						
Yes	5650	95 022	59.46	1.05 (1.02; 1.08)	1.10 (1.07; 1.13)	1.04 (1.01; 1.07)
No	417 711	10 832 806	38.56	ref.	ref.	ref.

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; PYR = person-years at risk.
*Adjusted for age at entry and sex.
†Adjusted for age at entry, sex, marital status, selected Charlson comorbidities, diabetes, hypertension, dyslipidemia, and chronic obstructive pulmonary disorder.

Table 7. HRs and 95% CI for All-cause Mortality and Composite CVD in Patients With Neovascular Age-related Macular Degeneration Exposed to VEGF Inhibitor Injections Within 60 Days Post-injection, Compared with Periods of Being Unexposed

VEGF Inhibitor	Deaths (n)	Follow-Up (PYR)	Mortality Rate (per 1000 PYR)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Fully Adjusted HR† (95% CI)
All-cause mortality						
Exposed periods‡	2225	92 725	24.00	0.24 (0.23; 0.25)	0.23 (0.22; 0.24)	0.26 (0.25; 0.27)
Unexposed periods§	10 645	85 960	123.84	ref.	ref.	ref.

VEGF Inhibitor	Events (n)	Follow-Up (PYR)	Incidence Rate (per 1000 PYR)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Fully Adjusted HR† (95% CI)
Composite CVD						
Exposed periods‡	2689	51 977	51.73	0.81 (0.77; 0.85)	0.81 (0.77; 0.85)	0.82 (0.78; 0.86)
Unexposed periods§	2961	43 045	68.79	ref.	ref.	ref.

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; PYR = person-years at risk.
*Adjusted for age at entry and sex.
†Adjusted for age at entry, sex, marital status, selected Charlson comorbidities, diabetes, hypertension, dyslipidemia, and chronic obstructive pulmonary disorder.
‡Exposed periods occur 60 days after injection.
§Unexposed periods span from 61 days post-injection until the next injection.

scenario, we may speculate that the reported risk of CVD in this study may actually be underestimated. In our main analysis, we observed a decreased HR for mortality, despite a high mortality rate among exposed compared with unexposed. This discrepancy may arise because the HR considers the age effect, which is not accounted for in the mortality rate. Consequently, the HR implicitly adjusts for age as a confounding factor because age is used as the underlying time axis. In a subgroup analysis, we observed a significantly reduced risk of all-cause mortality and CVD in patients with nAMD who were exposed to VEGF inhibitors within 60 days postinjection, compared with when they were unexposed. A previous study found that 20% of elderly individuals > 90 years of age discontinued treatment within 1 year and another study found that only 16% of elderly individuals > 90 years completed a 5 year follow-up.[26,27] We speculate that the observed decrease in all-cause mortality among often very elderly individuals may be influenced by the discontinuation of injection treatment, typically occurring > 60 days before their eventual death. This discontinuation, possibly due to fatigue and exhaustion, may in this analysis result in a smaller number of captured events, primarily limited to sudden deaths.[28] Our findings provide strong evidence for the high safety profile of intravitreal VEGF inhibitors in patients with nAMD, which has not

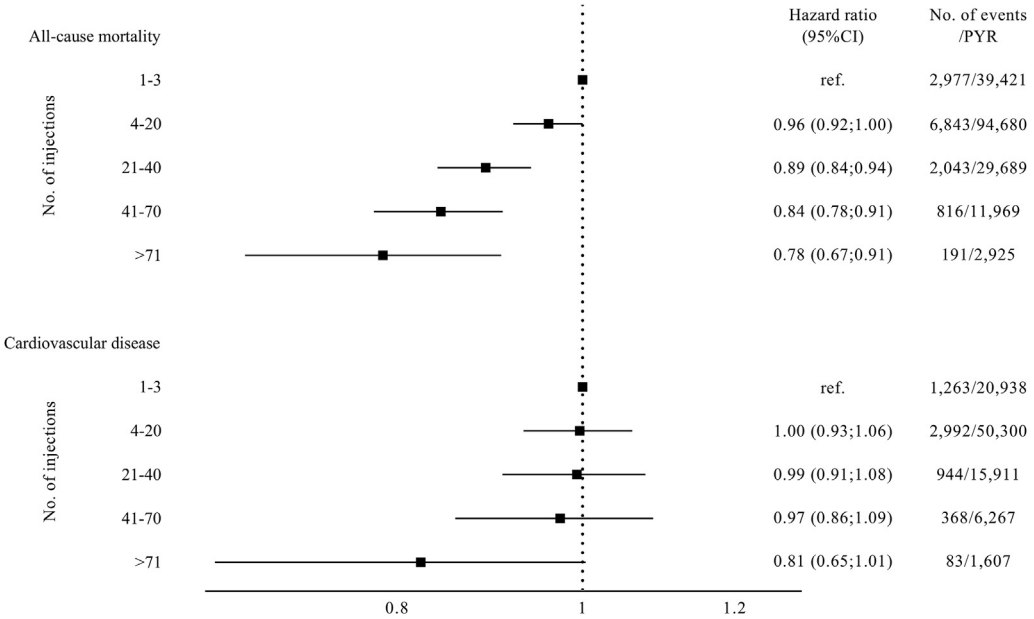

Figure 1. Hazard ratios and 95% confidence interval (CI) for all-cause mortality and composite cardiovascular disease in patients with neovascular age-related macular degeneration receiving VEGF inhibitors, stratified by number of injections and reported as adjusted for age at entry, sex, marital status, selected charlson comorbidities, diabetes, hypertension, dyslipidemia, and chronic obstructive pulmonary disorder. PYR = person-years at risk.

been previously confirmed in a large-scale nationwide population-based study. These results align with several large clinical trials conducted in the field of nAMD and retinal vein occlusion.[10,29–31] Also, a recent nationwide cohort study on retinal vein occlusion found no association between VEGF inhibitor treatment and all-cause mortality, even in patients with a history of CVD or other severe illnesses.[9]

One of the strengths of this study is the long follow-up time of 16 years. This extended duration allows for a comprehensive examination of outcomes and trends related to nAMD and its treatment. Still, it is important to acknowledge that changes may have occurred over this period regarding the administration of injections with VEGF inhibitors, the indications for treatment, and the registration of treatment. These factors may have introduced variability into the study results. The use of nationwide registers, which include data from all citizens, is indeed a significant strength as well. This reduces selection bias and provides a more comprehensive representation of the population with nAMD. Additionally, the fact that the treatment for nAMD is provided free of charge and only available at hospitals minimizes selection bias. Furthermore, the presence of a compensation system for hospitals based on correct registration to the nationwide register is also a strength. This system incentivizes hospitals to maintain accurate and up-to-date registration, resulting in reliable and high-quality data for the study.[32] The limitations of the study are also important to acknowledge. First, we were unable to distinguish between the specific VEGF inhibitor agents used in our study. During the study period, only ranibizumab and aflibercept were routinely used in Denmark. Previous studies have reported comparable risks between ranibizumab and aflibercept.[30] However, our results may not fully represent the safety profile of intravitreal bevacizumab therapy. Second, the absence of information regarding the administration of injections in 1 or both eyes limited our ability to assess the potential systemic double-dosing effect and its potential impact on the outcomes of our analyses. Third, the study lacks information on socioeconomic characteristics, which could be relevant factors influencing the outcomes. The lack of socioeconomic data hinders a comprehensive understanding of the influence of these variables, and it is possible to speculate that patients with personal resources to sustain the treatment course for an extended duration may belong to higher socioeconomic classes. However, it should be noted that the treatment is funded through a socialized tax-based health care model with universal coverage, which ensures access for all citizens without any out of pocket payment.

In conclusion, our analysis of 16 years of nationwide data revealed a decreased risk of all-cause mortality among patients with nAMD exposed to VEGF inhibitors. We observed a modest increase in the risk of CVD in the same group, but no increased risk was found when patients were grouped by number of doses or considered exposed within 60 days postinjection. These findings provide strong evidence supporting the safety of VEGF inhibitor treatment in terms of all-cause mortality and CVD in patients with nAMD aged $\geq$ 65 years.

Footnotes and Disclosures

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Analysis and interpretation: Thinggaard, Frederiksen, Grauslund, Stokholm
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Overall responsibility: Thinggaard, Frederiksen, Subhi, Möller, Sørensen, Kawasaki, Grauslund, Stokholm.

Abbreviations and Acronyms:
CI = confidence interval; **CVD** = cardiovascular disease; **HR** = hazard ratio; **nAMD** = neovascular age-related macular degeneration.

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References

1. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. 2018;392:1147−1159.
2. Rozing MP, Durhuus JA, Krogh Nielsen M, et al. Age-related macular degeneration: a two-level model hypothesis. *Prog Retin Eye Res*. 2020;76:100825.
3. Finger RP, Daien V, Eldem BM, et al. Anti-vascular endothelial growth factor in neovascular age-related macular degeneration - a systematic review of the impact of anti-VEGF on patient outcomes and healthcare systems. *BMC Ophthalmol*. 2020;20:294.
4. European Medicines Agency. Lucentis-H-C-715-II-0022: EPAR - assessment report - variation. https://www.ema.europa.eu/en/medicines/human/EPAR/lucentis#product-information-section; 2023. Accessed June 15, 2023.
5. Drugs.com. Lucentis FDA approval history. https://www.drugs.com/history/lucentis.html; 2023. Accessed June 19, 2023.
6. García-Quintanilla L, Luaces-Rodríguez A, Gil-Martínez M, et al. Pharmacokinetics of intravitreal anti-VEGF drugs in age-related macular degeneration. *Pharmaceutics*. 2019;11:365.
7. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br J Ophthalmol*. 2014;98:1636−1641.
8. 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;134:21−29.
9. Frederiksen KH, Stokholm L, Möller S, et al. VEGF inhibition in retinal vein occlusion does not associate with cardiovascular morbidity or mortality. *Ophthalmol Retina*. 2023;7:652−660.
10. Reibaldi M, Fallico M, Avitabile T, et al. Risk of death associated with intravitreal anti-vascular endothelial growth factor therapy: a systematic review and meta-analysis. *JAMA Ophthalmol*. 2020;138:50−57.
11. Reibaldi M, Fallico M, Avitabile T, et al. Frequency of intravitreal anti-VEGF injections and risk of death: a systematic review with meta-analysis. *Ophthalmol Retina*. 2022;6:369−376.
12. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. *Retina*. 2017;37:1847−1858.
13. Bressler NM, Boyer DS, Williams DF, et al. Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina*. 2012;32:1821−1828.
14. Thulliez M, Angoulvant D, Pisella PJ, Bejan-Angoulvant T. Overview of systematic reviews and meta-analyses on systemic adverse events associated with intravitreal anti-vascular endothelial growth factor medication use. *JAMA Ophthalmol*. 2018;136:557−566.
15. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449−490.
16. Nordic Health & Welfare Statistics. NCSP - classification of surgical procedures. In: *https://nhwstat.org/publications/ncsp-classification-surgical-procedures*; 2023. Accessed May 20, 2023.
17. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541−549.
18. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, et al. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46, 798−798f.
19. World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). https://www.who.int/standards/classifications/other-classifications/the-anatomical-therapeutic-chemical-classification-system-with-defined-daily-doses; 2023. Accessed May 17, 2023.
20. Hvidberg MF, Johnsen SP, Glümer C, et al. Catalog of 199 register-based definitions of chronic conditions. *Scand J Public Health*. 2016;44:462−479.
21. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173:676−682.
22. Chen X, Wang X, Zhang K, et al. Recent advances and clinical applications of deep learning in medical image analysis. *Med Image Anal*. 2022;79:102444.
23. Zhang XY, Guo XF, Zhang SD, et al. Comparison of bevacizumab and ranibizumab in age-related macular degeneration: a systematic review and meta-analysis. *Int J Ophthalmol*. 2014;7:355−364.
24. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119:2537−2548.
25. Dalvin LA, Starr MR, AbouChehade JE, et al. Association of intravitreal anti-vascular endothelial growth factor therapy with risk of stroke, myocardial infarction, and death in patients with exudative age-related macular degeneration. *JAMA Ophthalmol*. 2019;137:483−490.
26. Dhingra N, Upasani D, Ghanchi FD. Patterns of treatment discontinuation in patients receiving anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Indian J Ophthalmol*. 2022;70:2065−2070.
27. Subhi Y, Sørensen TL. Neovascular age-related macular degeneration in the very old (≥90 years): epidemiology, adherence to treatment, and comparison of efficacy. *J Ophthalmol*. 2017;2017:7194927.
28. Reinier K, Rusinaru C, Chugh SS. Race, ethnicity, and the risk of sudden death. *Trends Cardiovasc Med*. 2019;29:120−126.
29. Moja L, Lucenteforte E, Kwag KH, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2014;9:CD011230.
30. Plyukhova AA, Budzinskaya MV, Starostin KM, et al. Comparative safety of bevacizumab, ranibizumab, and aflibercept for treatment of neovascular age-related macular degeneration (AMD): a systematic review and network meta-analysis of direct comparative studies. *J Clin Med*. 2020;9:1522.
31. Maloney MH, Payne SR, Herrin J, et al. Risk of systemic adverse events after intravitreal bevacizumab, ranibizumab, and aflibercept in routine clinical practice. *Ophthalmology*. 2021;128:417−424.
32. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563−591.