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Real-life management of neovascular age-related macular degeneration (nAMD) in France: a nationwide observational study using retrospective claims data

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ABSTRACT

Aims: Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is standard care for neovascular age-related macular degeneration (nAMD), but the recommended monthly injection regimen is burdensome. Evidence suggests low injection/monitoring frequencies in clinical practice and suboptimal vision outcomes. This observational cohort study uses administrative claims data from the French national healthcare system to assess anti-VEGF treatment patterns and nAMD-specific healthcare resource demands and costs.

Patients and methods: nAMD patients ≥50 years initiating intravitreal ranibizumab, aflibercept or bevacizumab treatment (2014–2015), and propensity score-matched non-nAMD patients (controls), were identified from the Echantillon Généraliste de Bénéficiaires database. Outcomes of interest included anti-VEGF treatment patterns, and healthcare resource utilization and associated costs of patients vis-à-vis controls over 24 months.

Results: Study patients ($n = 355$) received (mean) 5.2 and 2.4 anti-VEGF injections over 0–12 and 12–24 months, respectively. Most patients (79.0%) remained on their initial anti-VEGF agent; among treatment switchers, the most common transition was from ranibizumab to aflibercept. During follow-up, nAMD patients were more likely than controls to require ophthalmology visits (99.7% vs. 44.8%), ocular procedures (optical coherence tomography/angiography/fundoscopy) (96.9% vs. 27.2%), cataract surgery (13.0% vs. 6.7%), and medical transports (38.0% vs. 31.9%). Mean numbers of ophthalmology visits (25.1 vs. 1.2) and medical transports (6.0 vs. 3.5) were higher ($p < .01$) among nAMD patients. Total reimbursed costs were two-fold higher for nAMD patients than controls (mean €16,799 vs. €8,255) due to higher treatment costs (€6,847 vs. €1,156), medical fees (€1,858 vs. €295), hospital fees (€6,396 vs. €5,235), and transport costs (€358 vs. €259). Excess total healthcare cost was (mean) €5,279 and €7,918 over the first 12 and 24 months of treatment, respectively.

Conclusions: Current intravitreal anti-VEGF treatment and monitoring requirements place a considerable economic burden on the French healthcare system. New intravitreal therapies with extended dosing intervals and predictable efficacy might reduce demand for ophthalmology services.

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Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision impairment and blindness among the elderly throughout the developed world[1] and has a profoundly detrimental effect on the independence and quality of life of affected individuals[2–4]. Neovascular or "wet" AMD (nAMD), characterized by macular neovascularization, intra- or subretinal exudation and hemorrhage, is the most aggressive form of the disease and accounts for the great majority (90%) of cases of AMD-related severe vision loss and blindness[5]. Advanced age is the major non-genetic risk factor for the development of AMD[6], and the prevalence and associated socioeconomic burden of the disease can be expected to increase as life expectancy improves. A recent meta-analysis of cohort studies from the European Eye Epidemiology consortium estimated that 13.2% of the European population aged ≥70 years had early AMD and 3.0% had late AMD during the period 1990–2013[7]. With regard to nAMD, the European Eye Study (EUREYE) reported an overall prevalence of 2.3% in Europeans aged ≥65 years[8]. Based on current French demographic data (13.6 million adults aged ≥65 years in January 2020)[9], this prevalence rate translates to approximately 312,000 adults in the ≥65-year age-group with nAMD in France. Projections from the Rotterdam Eye study data[10] suggest that in France,

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approximately 36,000 individuals develop advanced AMD each year, of whom 21,000 have nAMD[11].

The advent of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the management of nAMD over the past 15 years, not only stabilizing but in many cases reversing the vision damage caused by nAMD[12,13], and it is currently considered standard of care. Important considerations in ensuring optimal long-term vision outcomes with anti-VEGF therapy include the need for early initiation of treatment after nAMD diagnosis, appropriate intravitreal injection frequencies, and avoidance of treatment delays[14,15], which necessarily makes for protracted, intensive and costly treatment regimens. Currently, three anti-VEGF agents are prescribed for ophthalmological use in France: ranibizumab (introduced in 2007), aflibercept (introduced in 2013), and bevacizumab (granted a temporary use recommendation for the nAMD indication in 2015). Recent meta-analyses of direct comparative clinical trials of anti-VEGF agents in nAMD would suggest that ranibizumab, bevacizumab and aflibercept offer comparable efficacy in terms of their impact on visual acuity[16], and similar ocular tolerability profiles[16,17]. The frequent (typically monthly or bimonthly) intravitreal dosing regimens recommended for these agents are, however, difficult to sustain over the long term[18], and this has prompted the adoption of individualized, less burdensome *pro re nata* (*PRN*) and treat-and-extend dosing regimens in clinical practice[19,20].

Emerging therapies for nAMD, including sustained-release anti-VEGF formulations, long-acting anti-VEGF agents, agents that block non-VEGF pathways, sustained-delivery devices, and genetic therapies, offer the prospect of reduced treatment burden and improved vision outcomes[21]. Assessment of the likely impact that these therapies will have on real-world management of nAMD requires an understanding of current anti-VEGF treatment patterns and costs, which vary appreciably from country to country[15]. Information on the medical management, healthcare resource utilization, and associated costs of nAMD care in France is limited and often outdated, predating the era of anti-VEGF therapy[22–26]. This retrospective analysis of claims data was undertaken to provide an up-to-date picture of the epidemiology and treatment of nAMD, as well as an assessment of nAMD-specific healthcare resource demands and costs, in France.

Methods

This representative observational cohort study was based on de-identified administrative claims data sourced from the French national healthcare data system. The study was designed in collaboration with an Independent Scientific Committee and was exempt from legislation governing research in human subjects.

Data source

The French healthcare system is based on universal healthcare insurance coverage. As part of this structure, the national healthcare data system, SNIIRAM (Système National d'Informations Inter-Régimes de l'Assurance Maladie), now designated as the SNDS (Système National des Données de Santé), prospectively collects and links anonymized patient-level data from multiple sources, including reimbursed health expenses in primary care and claims paid by the national health insurance system to public and private hospitals. SNIIRAM/SNDS captures medical and administrative data from virtually all healthcare insurance plans, and currently covers 98.8% of the French population, making it one of the world's largest and most representative databases of its type[27,28]. SNIIRAM/SNDS provides information on all aspects of healthcare utilization and associated costs, including demographics, outpatient medical and paramedical care, hospital admissions, diagnoses, procedures, laboratory tests, chronic conditions, pharmacy prescriptions, medical transports, disability allowances, and sick leaves[28]. Cost information includes total costs and reimbursement costs, allowing healthcare expenses to be expressed from societal and national health insurance perspectives[28].

The EGB (Echantillon généraliste de bénéficiaires) claims database comprises a 1/97th randomly selected, representative sample of the SNIIRAM/SNDS database population (approximately 780,000 individuals)[28]. Patient data are stored and remain accessible for 20 years, making EGB the database of choice for longitudinal analysis of the more common chronic diseases[27].

Study population

The EGB database was screened to identify patients who received intravitreal anti-VEGF treatment between 1 January 2014 and 31 December 2017 (selection period). To avoid any immediate disruption to treatment patterns arising from the introduction of a new anti-VEGF agent, 2014 was chosen as the start of the selection period as this was the first year in which all three of the currently approved anti-VEGF treatments (bevacizumab, ranibizumab, and aflibercept) were available in France for the treatment of nAMD. Patient selection was terminated in 2017 since, at the time of the study (2019), this was the latest year for which information was available in the SNDS data system.

For study inclusion, patients were required (i) to be $\geq$50 years of age; (ii) to be continuously enrolled between 1 January 2009 and 31 December 2017 in a health insurance scheme integrated into the EGB database; and (iii) to have at least 2 reimbursement claims on separate dates between 1 January 2014 and 31 December 2017 for dispensation of ranibizumab [*Anatomic Therapeutic Chemical* (ATC) code S01LA04], aflibercept (ATC code S01LA05), or bevacizumab (temporary use recommendation) (ATC code L01XC07) associated with a diagnosis of degeneration of the macula and posterior pole [*International Classification of Diseases, Tenth Revision* (*ICD-10*) code H35.3) or a claim for intravitreal injection [*Classification Commune des Actes Médicaux* (CCAM) procedure code BGLB001] (Figure 1, Step 1). The date of the first recorded reimbursement claim for anti-VEGF treatment or intravitreal injection during the selection period was designated the index date. To ensure that anti-VEGF treatment

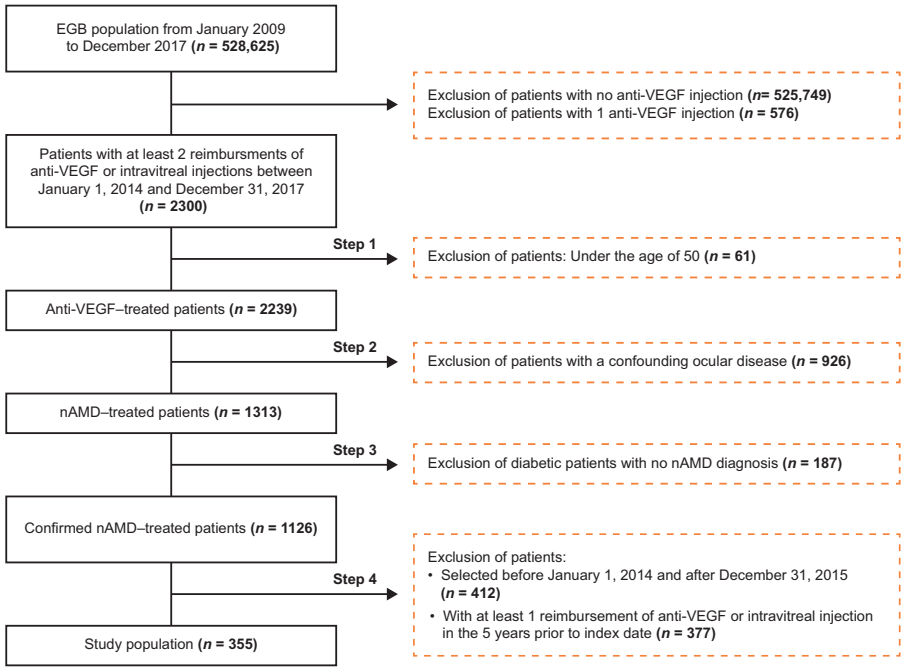

Figure 1. Patient selection algorithm.

was administered specifically for nAMD, the study excluded patients with an in-hospital or long-duration disease (LDD) diagnosis (2009–2017) of diabetes mellitus with ophthalmic complications (i.e. diabetic cataract and diabetic retinopathy) (*ICD-10* codes E10.3–E14.3), macular edema secondary to retinal vascular occlusion (*ICD-10* codes H34.0, H34.1, H34.2, H34.8, H34.9), or choroidal neovascularization secondary to pathologic myopia (*ICD-10* code H31.8), as well as patients with ≥1 claims (2009–2017) for intravitreal dexamethasone implant, or laser treatment specifically for diabetic retinopathy (Figure 1, Step 2). As a further safeguard, diabetic patients without an associated in-hospital or LDD diagnosis (2009–2017) of degeneration of the macula and posterior pole (*ICD-10* code H35.3) were excluded (Figure 1, Step 3).

Within the resulting population of anti-VEGF–treated nAMD patients, the subgroup of patients with newly diagnosed nAMD—defined as having no recorded reimbursement claim for nAMD in the 5 years before the index date—was identified (incident cases). For a description of treatment patterns and determination of healthcare resource utilization and associated costs, the index date for selection of the study population of incident nAMD patients was narrowed to the period between 1 January 2014 and 31 December 2015 to allow 2 years of follow-up after treatment initiation (Figure 1, Step 4).

A group of control subjects, comprising individuals aged ≥50 years who had no recorded diagnosis of nAMD and no reimbursement claim for anti-VEGF treatment or intravitreal injection between 2010 and 2017, was selected from the general population available in the EGB database in 2014–2015. To quantify the burden of nAMD, control subjects were matched and compared to study patients with incident nAMD (3:1 ratio of controls to patients) using individual propensity scores based on demographic and clinical variables (age, gender, region of residence, cardiovascular and respiratory disease history, and prior cataract surgery).

Outcomes

Baseline demographic and clinical characteristics of incident nAMD and control populations

Baseline sociodemographic characteristics (age, gender, geographic region of residence) and clinical characteristics, including Charlson Comorbidity Index (CCI)[29] at index date, medical history (cardiovascular disease, respiratory disease, diabetes, anxiety/depression, falls/fractures, glaucoma, cataract, diabetic retinopathy, and endophthalmitis) and ocular surgery history (glaucoma, cataract, retinal detachment, and endophthalmitis surgery) over the 5-year pre-index period, were described for patients with incident (2014–2015) nAMD and for propensity score-matched controls. CCI was based on 19 comorbidities weighted for severity and was adjusted for age[30]. Comorbidities of interest were identified from hospital discharge and LDD diagnosis (*ICD-10*) codes, medical procedure (CCAM) codes, and drug [ATC, *Unités communes de dispensation* (UCD), and *Code identifiant de Présentation* (CIP)] codes.

Anti-VEGF treatment patterns in the incident nAMD population

Anti-VEGF treatment patterns, including the type of anti-VEGF agent, number of intravitreal anti-VEGF injections administered and anti-VEGF treatment switches, were assessed at the patient level over the first 24 months post-index in the incident nAMD population. Anti-VEGF treatment switch was defined as a change from the use of treatment A to treatment B within 6 months after the previous intravitreal

injection, with no subsequent administrations of treatment A. Treatment switch-back was defined as the occurrence of a solitary injection of treatment B interspersed between sequential administrations of treatment A.

Healthcare resource utilization and costs in the incident nAMD and control populations

Hospitalizations of interest (myocardial infarction, thromboembolism, fall/fracture, and nAMD-related), emergency department, outpatient ophthalmology and general practice (all-cause) visits, ophthalmic procedures/examinations [optical coherence tomography (OCT), fluorescein/indocyanine green angiography, and fundoscopy], ocular surgery (glaucoma, cataract, retinal detachment, and endophthalmitis procedures), ophthalmic medication (intravitreal bevacizumab, ranibizumab and aflibercept, and topical antibiotic/antiseptic/corticosteroid eyedrops), sick leaves, and medical transports over the first 24 months post-index were compared between the incident nAMD population and control subjects. Event rates (mean number of events per patient) were calculated for the entire study population, regardless of follow-up duration ($\leq$24 months) and, where available, for those patients who completed 24 months of follow-up. Direct medical costs, including medical, surgical and paramedical (nurse, physiotherapist and orthoptist) fees, hospitalization, outpatient ophthalmology, pharmacy, medical transports, and sick leave costs reimbursed over this period were extracted from the EGB database and presented from the perspective of the French Health Insurance system. Cost comparisons between patient and control groups were conducted from 6 months pre-index onward to capture the additional cost of nAMD diagnosis. Costs were reported in Euros at 2018 values; costs that occurred prior to 2018 were adjusted to 2018 values[31]. Cost analyses were conducted in accordance with French National Authority for Health (Haute Autorité de Santé) guidelines on pharmacoeconomic evaluation[32].

Epidemiology of nAMD

The numbers of incident cases of anti-VEGF–treated nAMD identified in the EGB database population in 2014–2017 were extrapolated to provide an estimate of the number of people with incident anti-VEGF–treated nAMD in France during the same period. For this epidemiological analysis, the definition of "incident anti-VEGF–treated nAMD" was relaxed from that applied to the study population to allow inclusion of diabetic (non-DME) patients without an accompanying in-hospital or LDD diagnosis of nAMD (i.e. the Step 3 exclusion criterion was lifted; Figure 1). Adoption of this revised definition stemmed from concern that the requirement for an in-hospital or LDD diagnosis of nAMD was too restrictive, potentially resulting in underestimation of the actual number of nAMD-treated patients in the database population. Numerical projections were based on the ratio of the EGB database population on 1 January 2017 to the estimated French national population in 2017, and were adjusted to account for differences in the age and gender profiles of the two populations.

Statistical analyses

Continuous data were summarized as mean ± standard deviation values, and categorical data were presented as frequencies. Propensity scores of study patients and controls subjects were calculated using logistic regression. Variables included in the propensity score calculation were considered to be satisfactorily matched if the absolute standardized difference in value between the 2 groups was $<$0.1. Comparisons of healthcare resource use and costs between study patients and controls were performed using Yate's chi-squared test, Fisher's exact test, and Wilcoxon's signed-rank test. To reduce the influence of unobserved factors and selection bias on cost comparisons, difference-in-differences methodology, based on a comparison of the average change in costs over time between study patients and controls, was used to determine the differential effect of nAMD. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Study participants

Of a total of 528,625 adults continuously enrolled in the EGB database from 2009 to 2017, 2,239 patients aged $\geq$50 years had $\geq$2 reimbursement claims for ranibizumab, aflibercept, bevacizumab, or intravitreal injection during 2014–2017. After excluding patients with other possible indications for intravitreal anti-VEGF therapy, 1,126 patients were confirmed as receiving treatment specifically for nAMD over this period. Within this cohort, 355 patients were identified as initiating anti-VEGF treatment for newly diagnosed nAMD during 2014–2015 ('study population') (Figure 1), of whom 345 and 333 patients provided follow-up data at 12 and 24 months, respectively. Among the study population, 42 patients (11.8%) received their first and second intravitreal injections less than 3 weeks apart, suggesting possible bilateral disease in these cases.

The control group comprised 1,065 anti-VEGF treatment-naïve subjects with no recorded nAMD diagnosis, aged $\geq$50 years, who were propensity score-matched (3:1) to the incident nAMD population.

Baseline demographic and clinical characteristics of the incident nAMD and control populations

The study population ($n = 355$) had a mean age of 79.5 (range, 50–97) years at index date (baseline) and was predominantly female (65.9%) and geographically diverse, with the highest representation in the Ile-de-France, Auvergne-Rhône-Alpes, Grand Est, Hauts-de France, Normandie, and Nouvelle Aquitaine regions. The mean (SD) CCI score at baseline was 4.5 (2.0), with the majority of patients (87%) having a CCI score $\geq$3 (Table 1). Nearly one-half of patients (48.5%) presented with one or more long-term diseases during the 5-year pre-index period, including lymphatic or hematopoietic malignancies (13.5%), severe heart diseases such as heart

Table 1. Baseline demographic and clinical characteristics of the incident nAMD and control populations.

Characteristic	Incident nAMD ($N = 355$)	Control group ($N = 1,065$)
Age, years, mean (SD)	79.5 (9.5)	79.8 (9.7)
Age group, *n* (%)		
<70 years	61 (17.2)	N/A
70–80 years	83 (23.4)	N/A
80–90 years	167 (47.0)	N/A
>90 years	44 (12.4)	N/A
Gender female, *n* (%)	234 (65.9)	703 (66.0)
Geographic area, *n* (%)		
Île-de-France	51 (14.4)	141 (13.3)
Auvergne-Rhône-Alpes	44 (12.4)	125 (11.8)
Grand Est	37 (10.5)	101 (9.5)
Hauts-de-France	31 (8.8)	101 (9.5)
Normandie	30 (8.5)	97 (9.1)
Nouvelle-Aquitaine	29 (8.2)	98 (9.2)
Provence-Alpes-Côte d'Azur	27 (7.6)	80 (7.5)
Bretagne	25 (7.1)	92 (8.7)
Occitanie	24 (6.8)	66 (6.2)
Centre-Val de Loire	20 (5.6)	59 (5.6)
Pays de la Loire	19 (5.4)	50 (4.7)
Bourgogne-Franche-Comté	13 (3.7)	45 (4.2)
Other/unknown	5 (1.4)	10 (0.9)
Charlson Comorbidity Index, mean (SD)[a]	4.5 (2.0)	4.4 (1.8)
Medical conditions of interest in past 5 years, *n* (%)		
Cardiovascular disease	267 (75.2)	807 (75.8)
Anxiety/depression	137 (38.6)	N/A
Cataract	81 (22.8)	N/A
Glaucoma	51 (14.4)	N/A
Falls/fractures	35 (9.9)	N/A
Respiratory disease	24 (6.8)	75 (7.0)
Ocular procedures/surgeries in past 6 months, *n* (%)		
Ocular coherence tomography	322 (90.7)	53 (5.0)
Fluorescein/indocyanine green angiography	157 (44.2)	0 (0)
Fundoscopy	150 (42.3)	61 (5.7)
Cataract surgery	21 (5.9)	30 (2.8)
Glaucoma surgery	2 (0.6)	1 (0.1)

[a]Charlson Comorbidity Index, a weighted, age-adjusted estimate of mortality risk based on the presence and severity of 19 comorbid conditions, with higher Charlson Comorbidity Index scores correlated with reduced 10-year survival.
Abbreviations. nAMD, Neovascular age-related macular degeneration; N/A, Not available; SD, Standard deviation.

failure, cardiac arrhythmia, valvular and congenital heart disease (9%), and coronary artery disease (8.2%). The most frequent medical events of interest over this period were cardiovascular disease (75.2%), anxiety/depression (38.6%), fractures (6.8%), and falls (3.1%). One-third of patients (33.8%) had ≥1 ocular comorbidity, including cataract (22.8%) and glaucoma (14.4%). Almost all patients (95.8%) had received an ocular procedure/examination (OCT, fluorescein/indocyanine green angiography, and/or fundoscopy) during the 6-month pre-index period; a small minority (6.2%) had undergone ocular (predominantly cataract) surgery (Table 1).

The control group ($N = 1,065$) closely matched the study population with respect to the propensity score variables, namely age (mean 79.8 vs. 79.5 years), gender (34.0% vs. 34.1% male), geographic distribution, CCI score (mean 4.4 vs. 4.5), and presence of cardiovascular disease (75.8% vs. 75.2%) and respiratory disease (7.0% vs. 6.8%) (Table 1). The sole anomaly was a lower frequency of prior cataract surgery in the control group compared to the patient group (2.8% vs. 5.9%); however, the absolute standardized difference after propensity score matching was low (–0.17), suggesting that this variable was adequately balanced between the 2 groups.

Anti-VEGF treatment patterns in the incident nAMD population

Among the study population ($n = 355$), the most frequently administered anti-VEGF agent during follow-up (≤24 months) was ranibizumab (73.2% of patients), followed by aflibercept (43.1%) and bevacizumab (0.6%). Patients received their anti-VEGF injections predominantly in the outpatient setting (96.9%), and only occasionally as inpatients (8.7%). On average, each patient received 5.2 (SD 2.9) intravitreal anti-VEGF injections over months 0–12 ($n = 345$), and 2.4 (SD 3.3) injections over months 12–24 ($n = 333$).

For those patients with information on treatment continuity ($n = 343$), 79.0% ($n = 271$) remained on their initial (index) anti-VEGF agent during follow-up, whereas 11.7% ($n = 40$) experienced one switch of an anti-VEGF agent, 7.0% ($n = 24$) had an unknown number of treatment switches, and 2.3% ($n = 8$) had treatment switch-back. For patients with a single treatment switch ($n = 40$), the most frequent transitions were ranibizumab to aflibercept ($n = 31$, 75.5%) and aflibercept to ranibizumab ($n = 8$, 20%). The mean (SD) time to first switch after initiating anti-VEGF treatment was 8.8 (SD 6.0) months, and 72.5% of switches ($n = 29$) occurred within the first 12 months.

Table 2. Healthcare resource utilization during follow-up (≤24 months) in the incident nAMD and control populations.

	Incident nAMD patients ($N = 355$)	Control subjects ($N = 1,065$)	*p*-value
Outpatient visits of interest			
Patients with ≥1 visit, *n* (%)			
Any outpatient visit of interest	354 (99.7)	943 (88.5)	<.001
Ophthalmology	354 (99.7)	477 (44.8)	<.001
General practice	310 (87.3)	901 (84.6)	.243
No. unique visits per patient, mean (SD)			
Ophthalmology	25.1 (16.4)	1.2 (1.9)	<.001
General practice	8.9 (7.3)	8.6 (8.0)	.222
Emergency department visits			
Patients with ≥1 visit, *n* (%)	129 (36.3)	363 (34.1)	.479
No. unique visits per patient, mean (SD)	0.7 (1.2)	0.6 (1.1)	.319
Hospitalizations of interest			
Patients with ≥1 hospitalization, *n* (%)			
Any hospitalization of interest	49 (13.8)	122 (11.5)	.279
Myocardial infarction	7 (2.0)	10 (0.9)	.155
Thromboembolic event	8 (2.3)	26 (2.4)	1.000
Fall/fracture	33 (9.3)	97 (9.1)	1.000
nAMD	6 (1.7)	0 (0)	<.001
No. hospitalizations per patient, mean (SD)			
Hospitalizations of interest	0.2 (0.5)	0.1 (0.5)	.224
Days of hospital stay per year, mean (SD)[a]	1.6 (5.5)	1.5 (5.4)	.292
Sick leaves			
Patients with ≥1 sick leave, *n* (%)	4 (1.1)	10 (0.9)	.759
Days of sick leave per year, mean (SD)[b]	1.2 (12.7)	1.6 (26.8)	.753
Medical transports			
Patients with ≥1 transport event, *n* (%)	135 (38.0)	340 (31.9)	.041
No. unique events per patient, mean (SD)[a]	6.0 (32.7)	3.5 (27.6)	.006
Ocular procedures of interest			
Patients with ≥1 event, *n* (%)			
Ocular coherence tomography	340 (95.8)	161 (15.1)	<.001
Fundoscopy	170 (47.9)	184 (17.3)	<.001
Angiography	101 (28.5)	9 (0.8)	<.001
Ocular surgery of interest			
Patients with ≥1 event, *n* (%)			
Cataract surgery	46 (13.0)	71 (6.7)	<.001
Retinal detachment	3 (0.8)	0 (0)	.016
Glaucoma surgery	2 (0.6)	4 (0.4)	.644

Event rates are expressed for the overall population ($n = 355$ study patients; $n = 1,065$ control subjects) and are derived over a variable (≤24 months) follow-up period.
[a]Mean cumulative length of hospital stay among patients undergoing hospitalization ($n = 49$ for study patients; $n = 122$ for control subjects).
[b]Mean cumulative length of sick leave among the overall population ($n = 355$ study patients; $n = 1,065$ control subjects).
Abbreviations. nAMD, Neovascular age-related macular degeneration; SD, Standard deviation.

Most study patients (82.3%) were prescribed an adjunctive eyedrop for use with each intravitreal anti-VEGF injection; the most frequently prescribed medication types were topical antibiotics (71.0% of the study population), antiseptics (28.7%) and corticosteroid–antibiotic combinations (19.7%). In accordance with changes to guideline recommendations, the proportion of intravitreal anti-VEGF injections preceded by an antibiotic eyedrop prescription declined over the study period, from 67.1% in 2014 to 29.2% in 2017.

Healthcare resource utilization in the incident nAMD population

Outpatient visits, emergency department visits, and hospitalizations

Nearly all patients in the study population ($n = 355$) had one or more outpatient visits of interest (99.7%) during follow-up, including ophthalmology visits (99.7%) and general practice visits (87.3%), and 36.3% of patients had one or more emergency department visits (Table 2). Overall, 13.8% of patients had one or more hospitalizations of interest; this included hospitalizations due to falls/fractures (9.3%), thromboembolic events (2.3%), myocardial infarction (2.0%), and nAMD (1.7%) (Table 2). Over the entire 24 months post-index ($n = 333$), patients had on average 25.8 (SD 16.5) ophthalmology visits, 9.1 (SD 7.3) general practice visits, 0.6 (SD 1.0) emergency department visits, and 0.2 (SD 0.5) hospitalizations of interest. For hospitalized patients, the average total duration of hospital stay was 11.5 (SD 10.5) days per annum.

Ocular examinations/procedures

Almost all patients in the study population ($n = 355$) were documented as undergoing ≥1 ocular examination/procedure of interest (96.9%) during follow-up, including OCT (95.8%), fundoscopy (47.9%), and angiography (28.5%). On average, over 24 months post-index, users underwent 14.7 (SD 9.9) OCT, 5.4 (SD 6.0) fundoscopy, and 2.2 (SD 1.6) angiography procedures. A minority of patients underwent ocular surgery during follow-up (13.5%), including cataract surgery (13.0%), glaucoma surgery (0.6%), and surgery for retinal detachment (0.8%).

Sick leave and medical transports

Over the follow-up period, 38.0% of patients in the incident nAMD cohort had one or more reimbursed medical transports, and 1.1% of patients in this predominantly retirement-age population had one or more reported sick leaves.

Comparison of healthcare resource use and costs in the incident nAMD and control populations

Healthcare resource use

Healthcare resource utilization during follow-up was generally lower among control subjects than among patients with incident anti-VEGF–treated nAMD (Table 2). This was reflected in significantly smaller percentages of control subjects experiencing an outpatient ophthalmology visit (44.8% vs. 99.7%; $p<.001$), an ocular procedure (i.e. OCT, angiography, or fundoscopy) (27.2% vs. 96.9%; $p<.001$), cataract surgery (6.7% vs. 13.0%; $p<.001$), and medical transport (31.9% vs. 38.0%; $p=.041$), and, at the individual level, significantly fewer outpatient ophthalmology visits (mean 1.2 vs. 25.1; $p<.001$) and medical transports (mean 3.5 vs. 6.0; $p=.006$). In contrast, the proportions of patients with general practice and emergency department visits, non-AMD-related hospitalizations (i.e. admissions for myocardial infarction, thromboembolic events, or falls/fractures), and sick-leave absences were similar in the 2 populations, as were the average numbers of GP visits, emergency department visits, hospitalizations of interest, and sick days per patient (Table 2).

Healthcare costs

Total reimbursed costs per patient during follow-up were two-fold higher for the incident nAMD population (mean €16,799) than for the control group (mean €8,255) (Table 3). Compared with control subjects, patients with incident nAMD had higher treatment costs (mean €6,847 vs. €1,156 per patient) and medical fees (mean €1,858 vs. €295 per patient), but similar hospital fees (mean €6,396 vs. €5,235 per patient), paramedical fees (mean €1,309 vs. €1,321 per patient), transport costs (mean €358 vs. €259 per patient) and optical equipment costs (mean €5 vs. €4 per patient). For the incident nAMD population, treatment costs represented the largest percentage of all reimbursed costs (41%), followed by hospital fees (38%), medical fees (11%), paramedical fees (8%), and transport costs (2%) (Figure 2). Cost comparisons, which were adjusted to capture the additional cost of nAMD diagnosis in the study population, indicated significant increases in total costs of (mean) €5,279 per patient ($p<.05$) for study patients relative to controls over the period from 6 months pre-index to 12 months post-index and €7,918 per patient ($p<.0001$) over the period 6 months pre-index to 24 months post-index. These increases in total costs were attributable to significant ($p<.0001$) differential increases in treatment costs (mean €4,096 and €5,751 per patient) and medical fees (mean €1,061 and €1,612 per patient) over the −6 to 12-month and −6 to 24-month timeframes, respectively. In contrast, no significant divergence in hospital fees, paramedical fees, or transport costs was observed between study patients and controls over either period.

Epidemiological projections

Over the period 2014–2017, the number of incident cases of anti-VEGF–treated nAMD identified in the EGB database showed a slight year-on-year increase, rising from 200 (0.11% of the database population) in 2014 to 220 (0.12%) in 2015, 229 (0.13%) in 2016, and 247 (0.14%) in 2017. Projection of the most recent (2017) annual incidence figure to the national population resulted in an estimate of 34,134 (95% CI, 33,774 to 34,498) newly treated nAMD patients in France in 2017.

Table 3. Reimbursed healthcare resource costs (2018 Euro values) per patient during follow-up (≤24 months) for the incident nAMD and control populations.

	Incident nAMD patients ($N=355$)	Control subjects ($N=1,065$)
Hospitalizations and surgery		
Mean (SD)	6,396 (14,409)	5,235 (13,250)
Median (IQR)	490 (0–6,407)	22 (0–3,640)
Treatment		
Mean (SD)	6,847 (4,717)	1,156 (3,699)
Median (IQR)	5,602 (3,555–8,717)	561 (237–1,154)
Medical fees (outpatient visits)		
Mean (SD)	1,858 (1,686)	295 (296)
Median (IQR)	1,441 (810–2,298)	238 (108–390)
Paramedical fees (nurse, physiotherapist, orthoptist)		
Mean (SD)	1,309 (4,413)	1,321 (4,454)
Median (IQR)	117 (13–595)	57 (4–547)
Medical transports		
Mean (SD)	358 (1,994)	259 (2,575)
Median (IQR)	0 (0–202)	0 (0–104)
Optics		
Mean (SD)	5 (8)	4 (8)
Median (IQR)	0 (0–11)	0 (0–5)
Total cost		
Mean (SD)	16,799 (17,636)	8,255 (16,567)
Median (IQR)	11,565 (6,614–20,635)	2,010 (669–8,166)

Abbreviations. IQR, Interquartile range; nAMD, Neovascular age-related macular degeneration; SD, Standard deviation.

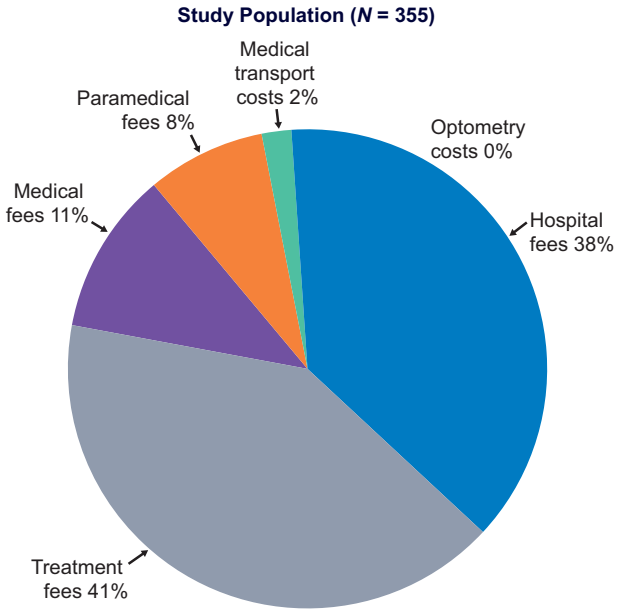

Figure 2. Distribution of reimbursed healthcare costs of study patients over 24 months of follow-up.

Discussion

The principal objective of this analysis of the EGB database was to provide a picture of anti-VEGF treatment patterns, healthcare resource demands, and associated costs specific to nAMD in the real-world setting. Consistent with the previous reports[15,18,33], our analysis of reimbursement claims indicates that ranibizumab was the most widely used anti-VEGF agent for the treatment of incident nAMD in French clinical practice during 2014–2017, followed by aflibercept, with bevacizumab used only rarely, and that the vast majority of intravitreal anti-VEGF injections (97%) were performed in the outpatient setting. It is also apparent from our analysis that despite regular patient follow-up (as reflected in a mean of 15.6 and 10.2 outpatient ophthalmology visits in Years 1 and 2, respectively) and regular monitoring of disease activity (mean 8.1 and 6.0 OCT examinations during Years 1 and 2, respectively), study patients were treated considerably less frequently (mean 5.2 and 2.4 anti-VEGF injections per patient during Years 1 and 2, respectively) than patients participating in randomized clinical trials of monthly, *pro re nata* (PRN), and treat-and-extend regimens such as ANCHOR, HARBOR, VIEW, TREX-AMD, CATT, and TREND[34–39]. Moreover, given that some 12% of the study population were possibly receiving bilateral anti-VEGF treatment, the mean injection frequency at eye level is likely to have been even lower. This finding is mirrored by previous real-world studies of anti-VEGF (predominantly ranibizumab) use in nAMD, which have indicated generally low injection frequencies (~4 to 6 per patient in the first year, and ~3 to 4 in the second year)[14,15,40–46]. Set against the backdrop of close ophthalmological monitoring, the low frequency of anti-VEGF injections in French clinical practice is indicative of increasing use by ophthalmologists of discontinuous (*PRN* and/or treat-and-extend) dosing strategies in the management of nAMD rather than to failings in patient follow-up.

An additional factor likely to influence anti-VEGF treatment frequency in routine clinical practice is the level of treatment reimbursement. As a country with a full reimbursement healthcare system, France may be expected to have higher intravitreal anti-VEGF injection frequencies and hence higher anti-VEGF treatment costs per patient than those countries operating under partial reimbursement or self-paid systems. The observational UNCOVER (Unraveling nAMD real-life Clinical management and Outcome with intravitreal Ranibizumab injection) study, which assessed intravitreal ranibizumab treatment patterns and vision outcomes in nAMD patients across various reimbursement scenarios in the Middle East, North Africa and the Asia Pacific region, reported average annual intravitreal injection frequencies (over a 1- to 3-year period) of 2.6 in self-paid, 4.1 in partially reimbursed and 4.7 in full reimbursed populations[47]. However, the average annual number of anti-VEGF injections received by patients in France remains low, particularly after the first year of treatment, suggesting that any reimbursement advantage is offset by other factors.

In keeping with previous reports that switching between anti-VEGF agents is uncommon in the treatment of nAMD[48], the analysis indicated that most (79.0%) study patients remained on their initial anti-VEGF agent for the duration of follow-up. When treatment switching did occur, it was implemented on average 9 months after starting treatment, and typically involved the replacement of ranibizumab (the most commonly used index treatment) with aflibercept.

Overall healthcare resource utilization over the 24-month follow-up period was higher for nAMD patients initiating anti-VEGF therapy than for propensity score-matched controls, as reflected in the greater proportions of study patients with outpatient ophthalmology visits, ocular procedures, cataract surgery, retinal detachment surgery, and medical transports. Most of this excess healthcare resource use occurred in the first year of treatment. The increased requirement for cataract and retinal detachment surgery among nAMD patients may be ascribed respectively to preferential ophthalmological screening resulting in more diagnoses of lens opacification, and the risk, albeit slight, of rhegmatogenous retinal detachment with intravitreal anti-VEGF therapy[49]. Of note, however, no differences were found between patients and their controls with respect to numbers of emergency department visits, non–AMD-related hospitalizations, and sick leaves.

Total reimbursed costs for incident nAMD patients exceeded those of control subjects by €5,279 per patient over the period from 6 months before to 12 months after initiation of anti-VEGF treatment and by €7,918 per patient over the period from 6 months before to 24 months after treatment initiation, with the largest contributors to this cost differential being treatment costs (mean excess €5,751 per patient over 2 years) and medical fees (mean excess €1,612 per patient over 2 years). Thus, the economic burden of nAMD management is mainly due to intravitreal anti-VEGF injection costs and patient monitoring costs, notably those arising from frequent ophthalmology visits and OCT procedures. In contrast, costs associated with the use of other

healthcare resources, such as hospital and paramedical services and medical transports, have marginal impact on the overall economic burden of nAMD.

Our analysis of the EGB database also provided the opportunity to estimate the current incidence of anti-VEGF-treated nAMD in France. Comprehensive national epidemiological figures for nAMD are required to assist proper planning for public health and ophthalmology policy makers. Since the EGB database does not specify the reason for administering anti-VEGF treatment, our approach was to identify all anti-VEGF–treated patients and then exclude those patients who may have received treatment for non-AMD–related indications (i.e. retinal vein occlusion, diabetic macular edema, diabetic retinopathy, and myopic choroidal neovascularization), as well as patients with nAMD coexisting with other retinal diseases. Numerical projections from the EGB database population, adjusted for gender and age differences, indicated that there were an estimated 34,134 incident cases of anti-VEGF–nAMD in France in 2017, representing 0.13% of the French population aged ≥50 years (estimated at 26.6 million in January 2020)[9]. Taking into account the different age profile of the various epidemiological survey populations, this estimate is broadly consistent with findings from the few published studies describing the incidence of nAMD in large, population-based cohorts in France. Thus, in the POLA (Pathologies Oculaires Liées à l'Age) study, a population-based prospective cohort study conducted in 1995–2000, the 3-year incidence of nAMD was reported to be 0.49% (95% CI, 0.13%–0.85%) among subjects ≥60 years of age[50]. As part of the European Eye Epidemiology (E3) Consortium, 2 French prospective cohort studies, ALIENOR-3C (Antioxydants, Lipids Essentials, Nutrition et Maladies Oculaires), conducted in 2006–2012 in subjects ≥70 years, and Montrachet-3C (conducted in 2009–2013 in subjects ≥75 years) reported crude prevalence rates for late nAMD of 5.6% and 2.2%, respectively[7]. Likewise, as part of the European Eye Study (EUREYE), a multinational cohort study to assess the prevalence of age-related maculopathy in the elderly, the participating French study centre (Paris-Creteil) reported a prevalence rate for nAMD of 3.0% among subjects ≥65 years of age[8]. Long-term follow-up findings from a small cohort of elderly (≥73 years) Bordeaux residents ($n = 659$) participating in the ALIENOR-3C study (2006–2012) indicated that the 5-year risk of incident nAMD in this population was 4.4%[51]. Overall, these findings would tend to suggest overall stability in the incidence and prevalence of nAMD in France over the past 20 years.

There are several limitations associated with the analysis of reimbursement claims, including potential shortcomings in the accuracy and completeness of the database record. Administrative claims databases are designed to manage healthcare transactions and generally do not provide comprehensive information on diagnoses, linked prescriptions, and clinical outcomes. In addition, ophthalmological datasets generally do not specify the laterality of treatment, which adds uncertainty to the interpretation of injection frequency and treatment switch data. (This is pertinent to our analysis since 12% of study patients were potentially receiving bilateral treatment.) A specific limitation of the EGB database is that it is underpowered to identify clinical events with low incidence rates. Moreover, in keeping with its specific purpose—to estimate the economic burden associated with management of incident nAMD with anti-VEGF therapy in clinical practice—the study excluded treatment-naïve patients and patients with concomitant ocular disease and is therefore likely to have underestimated the actual incidence of nAMD diagnosis in the French population. Finally, although attempts were made to ensure comparability of the study and control groups through propensity score-matching based on socio-demographic (age, gender, region of residence) and clinical variables (cardiovascular disease, respiratory disease, previous cataract surgery and Charlson comorbidity index), the quality of the matching may have been limited by a shortage of clinical data in the EGB database.

In conclusion, the high acquisition costs of current intravitreal anti-VEGF therapy, coupled with the requirement for regular (monthly or near-monthly) follow-up and monitoring of patients initiating such treatment for nAMD, place a considerable economic burden on the French healthcare system. Future intravitreal therapies that offer extended dosing intervals and predictable efficacy would have the potential advantage of reducing overall demand for medical services.

Transparency

Declaration of funding

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Declaration of financial/other relationships

AL and LD-B are employees of AbbVie, Inc. AM, JC, and SB are employees of stève consultants, which has a research consultancy agreement with AbbVie Inc.

J-FK has received consultancy fees from Allergan, Bayer, Janssen, Kanghong, Novartis, Novo Nordisk, Roche, Thea, and Zeiss. CD has received consultancy fees from Allergan, Bausch & Lomb, Laboratoires, Théa, Novartis, and Roche. CC-G reports consultancy fees from Thea; board membership at Allergan, Bausch & Lomb, Bayer, Novartis, and Roche; financial support from Bayer, Horus, and Novartis; and lecture fees from Bayer, and Novartis.

A reviewer of this manuscript has disclosed that they have received an honorarium for consultancy and lecture fees from Allergan, Bayer, Novartis and Roche. Another reviewer received consultancy fees from Bayer, Novartis and Roche Diagnostics and support fees from Bayer and Novartis. The other peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

AL, CD, CC-G, LD-B, and SB contributed to the conception and design of this study. AM, JC, and SB participated in data acquisition and analysis. All authors contributed to the interpretation of data, revised the manuscript critically for intellectual content, and approved the final version for publication. All authors meet the ICMJE authorship criteria and agree to be accountable for all aspects of the work.

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