Estimating the Yearly Number of Eyes with Treatable Neovascular Age-Related Macular Degeneration Using a Direct Standardization Method and a Markov Model

Jean-François Korobelnik, 1 Nicholas Moore, 2, 5 Patrick Blin, 2 Chandrabhan Dharmani, 4 and Gilles Berdeaux 5, 6

PURPOSE. To estimate the number of treatable eyes with neovascular subfoveal age-related macular degeneration (ARMD) in France.

METHODS. A literature search for studies documenting neovascular ARMD incidence rates and direct standardization according to age and gender were performed. Projection to the year 2025 was based on OECD (Organization for Economic and Co-operation Development) data. A cohort of patients aged 75 years was simulated by a seven-state Markov model. The mean treatment duration was fixed arbitrarily at 2 years. The probability of ARMD in the second eye was fixed at 30% at 5 years. Monthly mortality incidence was modeled from INSEE (Institut National de la Statistique et des Études Économiques) mortality tables. The time horizon of the model was 25 years. Sensitivity analyses were performed.

RESULTS. Based on the Rotterdam Study, 30,192 citizens per year will develop ARMD in one eye. Among them, 17,585 will be neovascular and 13,805 neovascular subfoveal ARMD. Taking into account the second eye, mortality, and a 2-year treatment duration, the number of neovascular subfoveal treatable eyes yearly would be 37,019 by 2025. Treatment duration was the most sensitive parameter. The number of eyes would be 18,899, 53,204, 67,535, and 80,162, for treatment lasting 1, 3, 4, and 5 years, respectively. A 2% yearly increase is expected up to 2025, due to population aging and the 1950s baby boom.

CONCLUSIONS. According to the study model, the yearly number of subfoveal neovascular ARMD treatable eyes in France will be 37,019 by 2025. Average treatment duration was the most sensitive parameter. (Invest Ophtalmol Vis Sci. 2006;47: 4270 – 4276) DOI:10.1167/iovs.05-1467

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duration, the probability of the fellow eye’s being affected by ARMD, the increasing death rate with advancing age. Last, population aging due to the 1950s baby-boom and longer life expectancy should be included. The present study was designed to estimate the total number of eyes affected by classic subfoveal neovascular ARMD that will be treated annually in France.

Materials and Methods

The study was performed in three steps: (1) identification of epidemiologic studies on ARMD; (2) first treated eye incidence rate direct standardization to include effect of age (the major risk factor of ARMD); and (3) construction of a Markov model to estimate the total number of neovascular ARMD treatments in France per annum, taking into account the mortality rate, the occurrence of treatable disease in the second eye, and treatment duration.

Literature Search

A comprehensive literature review was conducted by searching the PubMed database.24 Publications were searched from 1965 to June 2004. Search terms included age-related maculopathy (ARM), age-related macular degeneration (ARMD), neovascular ARMD, dry ARMD, atrophic ARMD, nonexudative ARMD, late ARMD, exudative ARMD, wet ARMD, soft drusen, large drusen, small drusen, pigmentary abnormalities, hyperpigmentation, hypopigmentation, increased retinal pigment, retinal pigment epithelial hypopigmentation, extrafoveal, juxtapapillary, subfoveal, incidence, prevalence, names of the relevant countries, predominantly classic lesions, minimally classic lesions, occult lesions, second-eye involvement, and progression from wet- to dry-form ARMD, along with epidemiologic terms and disease etiologies.

All articles retrieved by this process were screened for relevance to the present study. Case reports and animal studies were excluded. Any article that provided the incidence and/or prevalence of ARMD was further reviewed in detail. Priority was given to well-conducted, population-based epidemiologic studies that provided valid, reliable, and generalizable estimates of ARMD. The completeness of this search was checked against citations in published articles and by reviewing the published ARMD epidemiology literature in books.

A thorough Internet search was also conducted for further information on ARMD epidemiology. These were conducted via large search engines (e.g., Yahoo [http://www.yahoo.com], Google [http://www.google.com]) targeting both public and subscription-based medical Web sites (e.g., Medscape [http://www.medscape.com], MD Consult [http://www.mdconsult.com]). Articles that provided estimates on any of the searched terms were included for review and analysis for this study. Priority was given to well-conducted population-based epidemiologic studies which provided valid, reliable, and generalizable estimates. Studies were focused on France, but other countries were admitted. Articles had to report incidence or prevalence rates of neovascular ARMD by age groups, to permit direct standardization. Papers reporting incidence rates were favored, since current neovascular ARMD treatments should be initiated soon after the onset of disease. Reports of incidence or prevalence rates from visual impairment registries were ignored, because about half of all visually impaired patients do not register.4,5,26,27 Last, ARMD had to be medically confirmed, preferably according to the International Age-Related Maculopathy Epidemiologic Study Group rules.

Direct Standardization

Demographic data by age and gender, projected to 2025, was derived from United Nations data.27 Because gender is not a confounding factor for ARMD’s incidence or prevalence, direct standardization was conducted on age only. This allowed adjustment for age, when data concerned foreign countries, and took into account population aging when projections were made to 2025.

The Markov Model

A Markov model was developed (Tree Age Pro 2004; TreeAge Software Inc., Williamstown, MA), counting treatment months from diagnosis of ARMD in the first eye to the patient’s death. This method made it possible to estimate the annual number of treatable eyes, while taking into account treatment duration, death, and ARMD development in the second eye. A cohort of 1000 hypothetical patients entered the model with a new diagnosis of neovascular subfoveal ARMD in the first eye. Age was set at 75 years (the mean age of diagnosis of neovascular ARMD).9–15,17 The sex ratio was modeled as a 4th-order polynomial function of age, estimated from national demographic data.50 Hence the sex ratio of this cohort was country specific. The cohort was processed by the Markov model and followed up throughout 25 years, with a cycle duration of 1 month and death as the absorption state. Patients entered the model with treated neovascular ARMD in one eye and could change state at the end of each month. Three new states were possible: (1) treated disease in the second eye, (2) treatment stopped in one eye, and (3) death. Figure 1 presents a schematic design of the model.

Many studies evaluated the risk of development of an exudative lesion in the second eye. Some studies performed in the 1970s and 1980s1–36 reported frequency of development of neovascular ARMD in the second eye ranging from 3% at 1 year35 to 48% at 4 years.53 Annual incidence, estimated using a time-independent probabilistic model, varied from 3% to 15%.53 Other studies published later37,38 reported calculated (same method as above) annual incidence rates varying from 8% to 12%. We used a 7% annual incidence rate for our central scenario. Sensitivity analyses were performed to account for the uncertainty associated with this estimate.

A reference scenario fixed the average treatment duration at 2 years. Monthly probabilities were estimated using an exponential model. It was hypothesized that the duration of treatment for the second eye would be the same as the first. The monthly mortality incidence function is already published.59 Mortality tables per age and gender were collected from INSEE (Institut National de la Statistique et des Etudes Economiques). Yearly mortality was modeled as a function of intercept (–5.253), age-square (in year, 4.958 10−7), gender (1: male, 2: female; −1.385), and the age × square by gender interaction (1.271 10−3). Hence the mortality incidence rate of the cohort was country specific.

The Markov reward was the number of months under treatment. Reward was fixed to 1 month when one eye (either the first or the second) was treated and to 2 months when both eyes were treated during the same month. The number of treatable eyes/1000 patients was defined as the asymptotic value of the cumulative function of rewards over time.

Results

As mentioned, a comprehensive literature review was conducted by searching the PubMed database. These searches yielded 3671 articles. The abstracts of all these articles were reviewed for relevance, resulting in 304 relevant articles. Of these, we reviewed all articles published in English. For articles published in other languages, we reviewed their findings as reported in their abstracts. After thoroughly reviewing these 304 articles, 48 studies were considered relevant for inclusion in the analysis of this study.

Two studies were identified in France. A national study was performed in 1995 by the IPSEN Institute, to assess low vision. The objectives of this study were to estimate the incidence of low vision and related eye diseases presenting at ophthalmologists’ consultations. This study was not retained because neovascular ARMD was not clearly specified.

Delcourt et al. conducted the first large prospective population-based study (POLA) in France, evaluating the association of cardiovascular disease and its risk factors with ARMD,
and included both cataract and ARMD with their respective risk factors. These investigators predicted age- and gender-specific prevalence estimates of ARMD and its subtypes, in a sample of 2584 community residents aged 60 to 95 years. Definitions and diagnostic criteria were based on the International Classification of Diseases. However, the cross-sectional design of the survey did not permit an estimation of incidence rates.

Three studies were identified outside France that satisfied the selection criteria: the Rotterdam Study,42 The Blue Mountains Eye Study,43 and the Beaver Dam Eye Study.44 The Rotterdam Study was selected because, regarding the ARMD risk factors, French citizens are supposed to be more comparable (e.g., sun exposure, eating habits) to the Dutch than to Americans or Australians from the two other studies.

The Rotterdam Study reported neither the location (extrafoveal, juxtafoveal, or subfoveal) nor the type of neovascular lesion ARMD (classic versus occult). This information was not available neither for French nor European patients. The results reported by Moissieiev45 were not used, since data generated

### TABLE 1. Incidence (per thousand) of Dry and Neovascular ARMD According to the Rotterdam Study Results after 6.5 Years of Follow-Up

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Follow-Up in Person-Years</th>
<th>Dry</th>
<th>Neovascular</th>
<th>Dry + Neovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Incidence</td>
<td>Number</td>
</tr>
<tr>
<td>55–59</td>
<td>2,240</td>
<td>0</td>
<td>0.000</td>
<td>0</td>
</tr>
<tr>
<td>60–64</td>
<td>6,218</td>
<td>0</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td>65–69</td>
<td>6,602</td>
<td>3</td>
<td>0.454</td>
<td>2</td>
</tr>
<tr>
<td>70–74</td>
<td>5,460</td>
<td>3</td>
<td>0.549</td>
<td>7</td>
</tr>
<tr>
<td>75–79</td>
<td>3,578</td>
<td>5</td>
<td>1.397</td>
<td>9</td>
</tr>
<tr>
<td>80+</td>
<td>2,494</td>
<td>8</td>
<td>3.208</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>26,592</td>
<td>19</td>
<td>0.715</td>
<td>28</td>
</tr>
</tbody>
</table>

The Rotterdam Eye Study participants were classified according to the most advanced lesion in either eye, which explains why the numbers in the Dry + Neovascular columns correspond exactly to the sum of the Dry and Neovascular columns (i.e., no one was classified as having neovascular AMD in one eye and dry AMD in the other).

on the basis of the Macular Photocoagulation Study guideline did not fit our needs (e.g., the minimally/classic distinction and the type of lesions per localization were not addressed in detail). Olsen et al.46 and Margherio et al.47 reported this information in two cross-sectional surveys. There was good agreement on localization—that is, 82.7% of neovascular ARMD lesions were subfoveal according to Margherio et al., and 78.5% according to Olsen et al. However, discrepancies arose concerning the nature of the condition. According to Margherio et al. 54.0% of neovascular lesions were subfoveal and classic, whereas the proportion was 19.5% according to Olsen et al. Results will be presented according to both findings. Finally, it was hypothesized that these estimates were the same for the first and second eye.

Table 1 presents the yearly incidence per age group reported in the Rotterdam Study. Depending on the type of lesion, dry or neovascular, incidence rates increased exponentially with age.

Table 2 shows the population projection for France estimated by the United Nations. In the next 20 years, the population aged >55 years will increase by 29.2%.

Table 3 indicates the number of single-eye ARMD cases according to direct standardization, showing that 30,192 new cases should have appeared in 2005 (17,585 neovascular and 12,607 dry). The number of neovascular subfoveal ARMD eyes will lie between 3,429 and 9,498. In the next 20 years the number of neovascular subfoveal ARMD eyes lies between 37,019 and 39,000, and the number of classic neovascular subfoveal ARMD eyes between 13,805 and 14,543, and the number of classic neovascular ARMD at age 75 and subject to a 5-year second-eye treatment beyond 2 years was (97.5%). After an average treatment duration fixed at 2 years, the probability of treatment continuing beyond 5 years was 0.7 logMAR and a failure was defined by a loss of 3 lines48), whereas the proportion was 19.5% according to Olsen et al. However, discrepancies arose concerning the nature of the condition. According to Margherio et al. 54.0% of neovascular lesions were subfoveal and classic, whereas the proportion was 19.5% according to Olsen et al. Results will be presented according to both findings. Finally, it was hypothesized that these estimates were the same for the first and second eye.

Table 4 shows the cumulative number of treatable eyes over 5 years, among 1000 new patients per year with one eye already treated, according to age at diagnosis, treatment duration, and different incidence rates of neovascular ARMD in the second eye during the same period, as determined by our Markov model. With respect to our reference scenario (based on Fig. 2: average treatment duration 2 years, age at diagnosis 75 years, second-eye incidence rate 30% in 5 years) the projections in Table 3 should be multiplied by 2.682.

The Rotterdam Study provided first-eye incidence rates (Table 1). Table 4 gives the number of additional eyes that would be treated if the treatment duration is fixed at one year. For example, a population of 1000 persons diagnosed with neovascular ARMD at age 75 and subject to a 5-year second-eye incidence rate of 30%, followed up over their full life, would generate 369 second eyes needing treatment.

Table 5 presents results for France in 2005, projected to the end of the year. After 2 years of prior treatment and a second-eye 5-year incidence of 30%, the number of neovascular subfoveal eyes lies between 37,019 and 39,000, and the number of neovascular classic subfoveal eyes between 9,196 and 25,469.

### Table 2. French Population Demographics in 2005 with Projection to 2025 in Spans of 5 Years

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Current year 2005</th>
<th>2006-2025 Demographic Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>55–59</td>
<td>3,968,000</td>
<td>3,971,600</td>
</tr>
<tr>
<td>60–64</td>
<td>2,659,000</td>
<td>2,888,200</td>
</tr>
<tr>
<td>65–69</td>
<td>2,498,000</td>
<td>2,497,200</td>
</tr>
<tr>
<td>70–74</td>
<td>2,404,000</td>
<td>2,374,400</td>
</tr>
<tr>
<td>75–79</td>
<td>2,014,000</td>
<td>2,016,000</td>
</tr>
<tr>
<td>80–84</td>
<td>1,060,000</td>
<td>1,072,000</td>
</tr>
<tr>
<td>85+</td>
<td>1,227,000</td>
<td>1,270,000</td>
</tr>
<tr>
<td>Total</td>
<td>15,830,000</td>
<td>16,089,400</td>
</tr>
</tbody>
</table>

Source: United Nations.29

### Table 3. Yearly Incident Cases Using a Direct Standardization Approach, Applying French Demographics to Incidence Rates in van Leeuwen et al.42

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular + dry (van Leeuwen et al.45)</td>
<td>30,192</td>
<td>30,557</td>
<td>30,921</td>
<td>31,286</td>
<td>31,651</td>
<td>32,016</td>
<td>33,760</td>
<td>36,142</td>
<td>40,094</td>
</tr>
<tr>
<td>Dry (van Leeuwen et al.45)</td>
<td>12,607</td>
<td>12,769</td>
<td>12,931</td>
<td>13,094</td>
<td>13,257</td>
<td>13,419</td>
<td>14,395</td>
<td>15,208</td>
<td>16,664</td>
</tr>
<tr>
<td>Neovascular (van Leeuwen et al.45)</td>
<td>17,585</td>
<td>17,788</td>
<td>17,990</td>
<td>18,192</td>
<td>18,394</td>
<td>18,597</td>
<td>19,365</td>
<td>20,934</td>
<td>23,430</td>
</tr>
<tr>
<td>Neovascular subfoveal (Olsen et al.46)</td>
<td>13,805</td>
<td>13,963</td>
<td>14,122</td>
<td>14,281</td>
<td>14,459</td>
<td>14,598</td>
<td>15,202</td>
<td>16,433</td>
<td>18,922</td>
</tr>
<tr>
<td>Neovascular subfoveal classic (Olsen et al.46)</td>
<td>3,429</td>
<td>3,469</td>
<td>3,508</td>
<td>3,547</td>
<td>3,587</td>
<td>3,626</td>
<td>3,776</td>
<td>4,082</td>
<td>4,569</td>
</tr>
<tr>
<td>Neovascular subfoveal Margherio et al.47</td>
<td>14,543</td>
<td>14,710</td>
<td>14,878</td>
<td>15,045</td>
<td>15,212</td>
<td>15,379</td>
<td>16,015</td>
<td>17,312</td>
<td>19,376</td>
</tr>
<tr>
<td>Neovascular subfoveal classic Margherio et al.47</td>
<td>9,498</td>
<td>9,607</td>
<td>9,716</td>
<td>9,825</td>
<td>9,934</td>
<td>10,044</td>
<td>10,459</td>
<td>11,306</td>
<td>12,654</td>
</tr>
</tbody>
</table>

Subfoveal and classic subfoveal population sizes were estimated according to Olsen et al.46 and Margherio et al.47. Rates presented in the text should be applied from the neovascular population (from neovascular to neovascular subfoveal, from neovascular to neovascular classic).

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**Note:** The data and calculations in the text are based on the information provided in the document. Additional details and context have been added for clarity and completeness.
DISCUSSION

Direct standardization based on the Rotterdam Study,42 associated with a Markov model, was used to estimate the number of neovascular subfoveal ARMD treatable eyes in France, accounting for mortality, treatment duration, age at diagnosis, and the probability of ARMD in the second eye. We used the United Nations'29 demographic projection for 2025 to identify future needs. According to our reference scenario (average treatment duration of 2 years, age at diagnosis 75 years, and second-eye incidence rate 30% in 5 years) neovascular subfoveal ARMD eyes totaling 37,019 to 39,000 should have needed treatment in 2005, of which 9,196 to 25,469 should have been classic. The cases will increase by 1% per annum until 2025.

A comparison with the verteporfin HTA reports21–24 is not straightforward because we did not use the same methods, and our results are expressed as number of treatable eyes, whereas the HTA reports describe number of patients. We believe that the use of incidence rates, instead of dividing prevalence by average disease duration to derive a proxy for the incidence rate, is a more appropriate method, especially with neovascular ARMD where age plays a predominant role. Also, the second eye contributes significantly to the number of treated eyes. If the bilateral nature of the disease is overlooked, the resources needed to treat patients adequately are underestimated by about one third.

The Olsen et al.46 paper was published after the publication of the HTA reports. If this article has confirmed the frequency of subfoveal localization, reported by Margherio et al.,47 a dramatic discrepancy exists in the rate of classic neovascular lesions. Olsen et al.46 themselves discussed a variety of selection biases to explain the acknowledged difference. More data are needed to resolve this uncertainty about the number of treatable subfoveal classic eyes.

Our approach has several limitations. We used Dutch data as a proxy for French data so that we could use incidence estimates rather than prevalence estimates. The French POLA survey,41 projecting a life expectancy of 10 years after the diagnosis of ARMD, would have given similar results. In our attempt to evaluate treatment needs in 2025 we hypothesized a constant incidence of neovascular ARMD per age group, which somewhat contradicts an RNIB (Royal National Institute of the Blind) report.8 Some strong hypotheses were built into our Markov model: (1) equal treatment duration for both eyes; (2) treatment probability independent of age; (3) treatment failure probability, an exponential function; (4) independent disease evolution in the two eyes; (5) independence of visual impairment and death; and (6) no bilateral disease at entry into the model. Some refinements could be added to the model should it be combined with a full stochastic approach, but the sensitivity analyses in Table 4 has taken into account the three major variables contributing to outcome: age at diagnosis, treatment duration, and 5-year second-eye incidence rate.

Apart from sex ratio and mortality incidence rates, no other data in our model were country specific. Life expectancy and the age structure are very similar across 15 of the EEC countries49 (excluding eastern European Union countries). Therefore, the estimations in Table 4 may be used for countries other than France.

### TABLE 4. Number of Treatable Eyes among 1000 New Neovascular ARMD Cases Per Annum in France

<table>
<thead>
<tr>
<th>Fellow Eye 5-Year Incidence Rate (%)</th>
<th>65 Years</th>
<th>75 Years</th>
<th>85 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>10</td>
<td>1193 2401 3536 4596 5577</td>
<td>1082 2141 3091 3937 4685</td>
<td>960 1828 2539 3120 3596</td>
</tr>
<tr>
<td>20</td>
<td>1395 2792 4101 5319 6444</td>
<td>1243 2441 3513 4463 5302</td>
<td>1067 2018 2794 3425 3941</td>
</tr>
<tr>
<td>30</td>
<td>1533 3063 4497 5832 7065</td>
<td>1369 2682 3854 4892 5807</td>
<td>1163 2191 3027 3706 4260</td>
</tr>
<tr>
<td>40</td>
<td>1627 3249 4774 6195 7510</td>
<td>1468 2872 4128 5240 6220</td>
<td>1250 2348 3241 3965 4556</td>
</tr>
<tr>
<td>50</td>
<td>1690 3377 4968 6453 7830</td>
<td>1545 3023 4347 5521 6556</td>
<td>1327 2491 3438 4204 4830</td>
</tr>
</tbody>
</table>

Data are shown according to age at diagnosis, treatment duration (1–5 years), and second-eye 5-year incidence rate. The estimation was performed by a Markov model (see Figs. 1, 2).
than France, with a fair approximation. We also tried to provide sufficient estimates to permit a reasonable linear extrapolation. However, we advise use of an exponential extrapolation, which would give less biased results as our estimates came from a multiplicative model.

New drug classes for neovascular ARMD will become available after verteporfin. It may be that drug combinations and cyclical treatment will be used, as with other chronic diseases, such as cancer. These developments may preserve visual acuity for a longer time, but lengthy treatment would call for additional resources. Table 4 can be used to estimate the incremental resources required. For example, a new drug necessitating administration for more than 3 years instead of 2 years, would incur serious consequences for patient care delivery 20 years hence. In conclusion, the allocation of resources to neovascular ARMD should cover the bilateral extension of the disease. New drugs will have an impact on treatment duration, and this should be anticipated by public health decision makers. To neglect now the long-term trend of increasing incidence will incur serious consequences for patient care delivery 20 years hence. Finally, much uncertainty remains as to the incidence rate of classic neovascular subfoveal ARMD. If public health decision makers want to consider this subgroup of patients as a potential target population, additional epidemiologic work must be done.

References

8. Royal National Institute for the Blind. Office of National Statistics mid-1996 population estimates, estimates for 1996 of visually impaired people (ie, registrable) and the number of people registered blind and partially sighted as at 31st March 1997 in the UK.
20. Hjelmgren J, Berggren F, Andersson F. Health economic
17. D'Amico DJ, Goldberg MF, Hudson H. Anecortave acetate as
15. Blinder KJ, Blumenkranz MS, Bressler NM, er al. Verteporfin ther-