Public Health Impact of Neovascular Age-Related Macular Degeneration Treatments Extrapolated from Visual Acuity

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PURPOSE. To estimate the potential public health impact of treatment with new medications intended to preserve vision in patients with neovascular age-related macular degeneration (AMD).

METHODS. A Markov model was used to simulate the natural history of AMD over the lifetime of patients with diagnosed neovascular AMD from clinical trials and epidemiologic surveys. It applied to a cohort of patients aged 75 years, with newly diagnosed neovascular AMD in one eye, whose visual acuity was 0.7 logMAR. Probabilities were calculated for the risk of AMD in the remaining eye and for premature mortality. Results of the model were expressed as the duration of low vision (worse eye VA>1.0 and better eye VA>0.7 logMAR) and blindness (bilateral VA >1.0 logMAR). Health consequences of blindness and low vision were estimated for depression, hip fractures, institutionalization, and life expectancy.

RESULTS. For AMD patients with a 50% probability of VA >1.0 logMAR at 1 year, in one eye, the probability of lifetime bilateral blindness was >47%. The patients would live approximately 7 years with monocular vision >1.0 logMAR and an additional 4 years with bilateral blindness and a >15% probability of depression due to AMD. Life expectancy was decreased by approximately 2 years, >90/1000 patients would sustain a new hip fracture, and 1.5% of the patients would require institutional care for visual impairment due to AMD. To achieve a defined public health outcome (visual impairment and consequent comorbidity), it was necessary for the VA effectiveness of new treatments to increase in parallel with disease severity.

CONCLUSIONS. Comorbidity related to visual impairment contributes significantly to the public health impact of AMD. Aggressive lesions need highly effective treatments. Models may be used to compare the public health impact of placebo-controlled clinical trial results. (*Invest Ophthalmol Vis Sci.* 2007; 48:96–103) DOI:10.1167/iovs.06-0283

Age-related macular degeneration (AMD) is the most common cause of adult blindness in Western, developed countries.[1,2] Late-stage AMD exists in two forms: atrophic and neovascular exudative. Blood or serum leakage resulting from choroidal neovascularization (CNV) may occur precipitously and is often associated with an abrupt loss or distortion of vision.[3] AMD occurs predominantly in older people and significantly impairs their quality of life and functional independence.[4] The burden of ocular morbidity and visual disability due to AMD will increase further with an increasingly older population and if there is no reduction in its incidence or improvement of treatment. A steady increase in the number of people registering as blind in most Western countries suggests that AMD is increasing.[5] Yet, despite the public health impact of current AMD, no attempt has been made to quantify its burden over a patient's lifetime.

A few, mainly physical, treatments for neovascular AMD designed to arrest leakage from CNV have been explored, but most results are disappointing. A more recent procedure (photodynamic therapy: PDT) in which a photosensitive drug and low-energy laser are used has produced clinically meaningful and statistically significant effects, compared with placebo (i.e., a visual acuity [VA] loss of <15 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart). As a consequence, verteporfin (Visudyne; Novartis, Basel, Switzerland) has been launched in most developed countries. Its efficacy has been demonstrated by the TAP (*T*reatment of *A*ge-related macular degeneration with *P*hotodynamic therapy)[6-10] and VIP (*V*erteporfin *I*n *P*hotodynamic trial) study groups.[11] In late 2004, the U.S. Food and Drug Administration approved pegaptanib (Macugen; Pfizer, New York, NY), a vessel endothelial growth factor inhibitor administered intravitreally for neovascular AMD.[12] Studies demonstrated AMD stabilization (defined as a <3-line loss on the ETDRS chart) with both drugs. Although considerable variability (46%–60%) was found in the placebo response rates of the different trials, both drug treatments (PDT and Macugen) were consistently superior to placebo (approximately 15%). Other treatments, with other mechanisms of action, are currently in development or were approved recently by the FDA (e.g., ranibizumab, Lucentis; Genentech, S. San Francisco, CA).

After marketing authorization, the next major step is a cost-effectiveness analysis for pricing and reimbursement negotiations. The West Midlands Health Technology Assessment Collaboration (UK) conducted a comprehensive economic study[13] of PDT for neovascular AMD, as demanded by the National Institute for Clinical Excellence (NICE).[14] The West Midlands model included the public health impact of blindness and its related consequences, specified as depression and new hip fractures. However, the time horizon was restricted to 2 years (TAP trial duration), and only the treated eye was considered, thus ignoring the bilateral nature of the disease.

A survey of different clinical studies in neovascular AMD shows it to be a complex multifactorial disease. Many parameters influence its evolution, such as clinical lesion characteristics (predominantly classic, minimally classic, and occult CNV), lesion location (subfoveal, juxtafoveal, extrafoveal), lesion size, and VA at diagnosis. Combinations of parameters make some lesions more aggressive than others and partially explain the apparent variability of placebo response rates.

The major public health outcome of AMD is blindness. Hence, public expenditure should be commensurate with the availability of treatments that minimize visual impairment. From a strictly health economics point of view, it would be legitimate to increase the resources to treat aggressive lesions when justified by the clinical evidence. Maintenance therapy that avoids or postpones acute exacerbations would also bring added value by preserving a patient's visual status. Such treatment strategies, however, would need to be evaluated before they are implemented. The present study estimates the public health outcomes of potential treatment strategies aimed at controlling a patient's lifetime VA, when the bilateral nature of neovascular AMD is taken into account.

MATERIAL AND METHODS

Morbidity and Mortality Associated with Blindness

A literature search, from 1965 to December 2004, was conducted in the PubMed database (National Library of Medicine, United States of America)[15] to identify associations between blindness and morbidity/mortality, after taking into account the many morbidities that afflict elderly populations. References published in the PDT Health Technology Assessment Reports were also checked.[13,16-18] All articles retrieved by these procedures were screened for their relevance to the present study. The completeness of this search was checked against citations in published articles.

The familiar association of falls and hip fractures with visual impairment is reported by numerous papers, and we estimated it from Legood et al.,[19] who made a comprehensive literature review and identified 20 surveys from 1980 to 2000.

Six papers have also reported frequent association between blindness and depression.[20-25] In addition, an excess of premature mortality associated with blindness was demonstrated.[26-31] Estimates included in our model were based on a French national longitudinal study of handicaps.[32]

Last, institutionalization, as identified by Brézin et al.,[33] is an additional health outcome associated with blindness.

Markov Model

Design of the Model. The purpose of a public health impact model is to simulate accurately and credibly the natural course of a disease and to investigate the impact of treatments, or events, on predefined clinical outcomes. To do so, it is necessary to describe, first, the natural history of the untreated disease in terms of health states from onset to cure or death and, second, the existing treatment options with respect to their expected effects.

Markov models are often used to simulate the progression of long-term chronic diseases.[34] A Markov model is fully defined by a set of independent clinical states. Values of outcome, cost, and comorbidities, are ascribed to each state and accumulated over time. According to the natural history of the condition, and the results of medical procedures, patients move between health states over time (divided into periods or cycles) according to probabilities defined by the transition probabilities matrix. An absorbing state must also be defined— that is, a state that patients cannot leave once entered into the model (death in the case of our model). The probability of switching between states is assumed to be independent of previous states. This provision constitutes the so-called without-memory feature of Markov models. We used a Monte Carlo first-order microsimulation with tracker variables, to permit memorization. The simulation followed individuals throughout the model, one at a time, so that tracker variables could record each person's history. The average of multiple individual trials simulates the calculation of an expected value.

Markov State Definition. Markov modeling was performed with commercial software (Data Pro 2004; Tree Age Software Inc.,
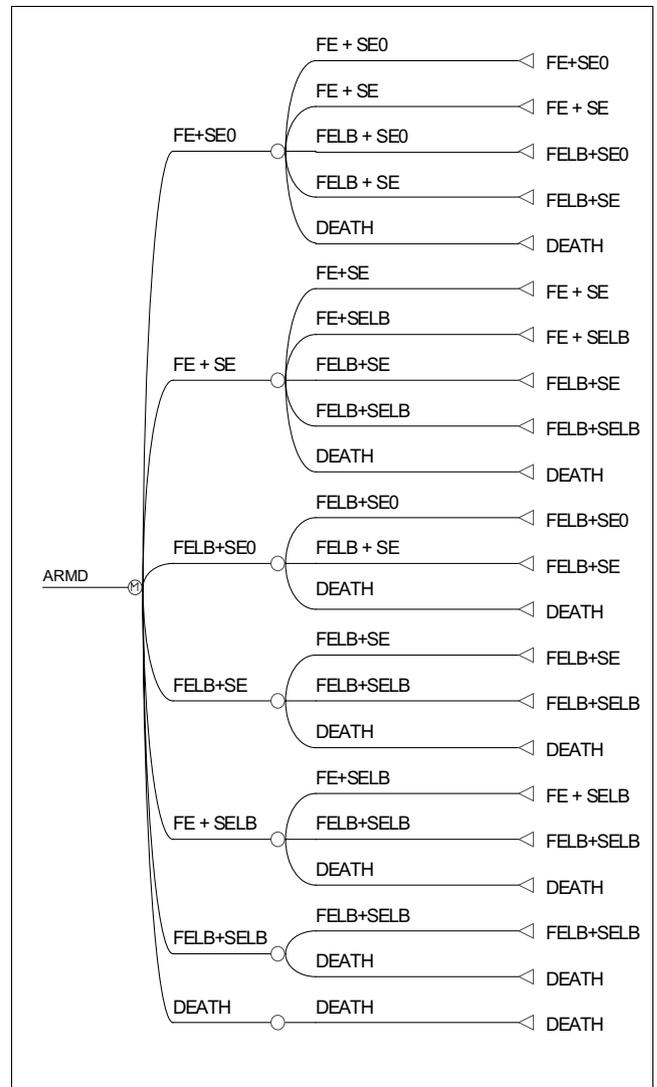

FIGURE 1. Markov state model description.

Williamstown, MA). The model (Fig. 1) included the following seven states: (1) first eye affected and second eye spared (FE+SE0); (2) first and second eyes affected (FE+SE); (3) first eye legally blind and second eye spared (FELB+SE0); (4) first eye legally blind and second eye affected (FELB+SE); (5) first eye affected and second eye legally blind (FE+SELB); (6) first and second eyes legally blind (FELB+SELB); and (7) death as the absorbing state.

The Markov states were created for model definition and were not conceived as clinically recognized states. Accepted clinical states, such as blindness and unilateral versus bilateral AMD, can be derived from the Markov states.

Time Horizon. A cycle of 1 month was considered appropriate for the model, as the evolution of AMD and the transition from low vision to blindness can occur in such an interval. The model began at time 0 with a cohort of patients characterized by the following features: age 75 years (mean age at diagnosis reported by most clinical trials[6-12]), sex-ratio 1.39 women:1 man, and 0.7 logMAR VA (Snellen 10/50) for an eye affected by AMD. Patients were followed up over 25 years (300 cycles) to simulate completely the cohorts' progression from diagnosis to death.

Transition Probabilities. All patients entered the model in the FE+SE0 state. Table 1 describes the transition probabilities matrix. Monthly probabilities were derived by an exponential function.

TABLE 1. Markov State Transition Probability Matrix

| | | First Eye Treated (FE) | | | First Eye Legally Blind (FELB) | | | |
| | | Second Eye without AMD (SE0) | Second Eye Treated (SE) | Second Eye Legally Blind (SELB) | Second Eye without AMD (SE0) | Second Eye Treated (SE) | Second Eye Legally Blind (SELB) | Death |
Time t	Time (t + 1)							
FE	SE0	†	P (2nd eye)	0	P (blind)	P (blind)* P (2nd eye)	0	P (death)
	SE	0	†	P (blind)	0	P (blind)	P (blind)*P (blind)	P (death)
	SELB	0	0	†	0	0	0	P (death)
FELB	SE0	0	0	0	†	P (2nd eye)	P (blind)	P (death)
	SE	0	0	0	0	†	P (blind)	P (death)
	SELB	0	0	0	0	0	†	P (death)
Death		0	0	0	0	0	0	1

The probability that one eye would be blind at 1 year (P (blind)) was subject to a full sensitivity analysis (10%, 30%, 50%, and 70%) and considered to be an indicator of the severity of disease progression. The 5-year probability of the disease's developing in the second eye was taken from Reference 35 and fixed at 30%. The death probability was estimated from national statistics published by INSEE (Institut National de la Statistique et des Etudes Economiques)[37] and has been used elsewhere.[38]

† 1 minus other probabilities.

The probability that the second eye (P (2nd eye)) would be affected at year 5 was estimated as 30%.[35] The probability of unilateral blindness (P (blind)) was synonymous with VA's deteriorating in the affected eye to ≥1.0 logMAR (Snellen 10/100). A theoretical set of unilateral blindness probabilities (sensitivity analysis) was used to provide outcomes corresponding to the severity and rapidity of disease progression. Probabilities of unilateral blindness during year 1 increased by 10% steps from 10% to 70%. The range was fixed arbitrarily, after checking that values >70% would not alter the results dramatically. Age and sex are well known predictors of death (cf. national mortality table for France).[36] Mortality rates for persons older than 50 years were extracted and modeled according to age squared, sex, and interaction. As the sex ratio varies with age, the model used a fourth-order polynomial function based on data from INSEE (*Institut National de la Statistique et des Etudes Economiques*).[37] This mortality function has been used previously.[38]

Markov Model Health Outcomes. Monocular vision was defined as one eye with VA >1.0 logMAR. Blindness was defined as both eyes worse than 1.0 logMAR. Low vision was defined as one eye affected and the second with VA >1.0 logMAR (FELB+SE or FE+SELB). The foregoing definitions of blindness and low vision do not necessarily correspond to definitions of "legal blindness," as used variously worldwide, and the reader should bear this in mind when interpreting the results. Models are used to simplify reality and the present model used a restricted definition of visual impairment specifying VA values.

Health outcomes (hip fracture, depression, and institutionalization) were allocated to binocular blindness (FELB+SELB) and to blindness in one eye and low vision in the other (FELB+SE or FE+SELB). Outcomes were adjusted on the national incidence of health outcomes (French data in the present case).

Microsimulation was used to estimate the consequences of visual impairment on the stated outcomes, in terms of prevalence rates. People with rapidly deteriorating vision tend to become either depressed or more depressed by their condition. Galaria et al.[39] studied patients with low VA in one eye who subsequently lost vision in the second eye. They found that 25% of patients became depressed at the onset of low vision in the second eye. However, 6 months later more than one third of patients were having new episodes of depression. The overall probability of becoming depressed because of loss of vision was estimated as 38.6% after 1 year. This probability was introduced into our model when blindness had persisted for at least 12 months, and it was used to estimate the degree of depression related to blindness.

The model associated the hip fracture rate with both blindness (FELB+SELB) and the two low vision states (FELB+SE; FE+SELB). To take account of national differences in morbidity incidence rates, the baseline probability of hip fracture in the general population with unimpaired vision was estimated from a published French study[40] that reported a rate of 1.09% *PA* for women aged ≥75 years, and a European study[41] with rates of 0.9% *PA* for patients aged 65 to 69 years and 1.4% *PA* for patients aged 70 to 74 years. Risk rates for new hip fractures due to blindness and low vision were estimated from Legood et al.[19] and were 1.9% and 1.6% *PA*, respectively. Transformation of these data into relative risk was performed as described by Bouyer et al.,[42] and from this the number of hip fractures related to visual impairment was estimated. The extrapremature mortality associated with blindness and monocular low vision states was estimated from one study.[32] The mortality odds ratio (OR) for blindness was 2.79 and for low vision, 2.06. Relative risk rates were derived from the OR.[42]

Institutionalization rates associated with the blindness (FELB+SELB) and monocular vision states (FELB+SE; FE+SELB) were estimated by Brézin et al.[33] The odds ratio for blindness was 3.268 between 60 and 80 years of age and 0.305 after 80 years. Odds ratios for low vision were estimated at 2.827 and 2.055, respectively. The annual prevalence of institution calculated from the Brézin study was estimated at 1.143%.

RESULTS

Figure 2 shows the probabilities of entering one of the seven clinical states over time and the probability of VA >1.0 logMAR at 1 year. The probability of death increased monotonically from 0 to almost 1 and followed a sigmoid curve. The probability of blindness in one eye, with no disease in the other, increased during the first 3 to 5 years after disease onset. The probability of bilateral VA deteriorating >1.0 logMAR reached a plateau between years 9 and 15. The apparent decline of both curves after year 17 was mainly due to the greater probability of death with increasing age.

Table 2 presents Markov model results for the probability of VA >1.0 logMAR developing in an affected eye. The average baseline VA of patients receiving placebo in controlled clinical trials was 0.7 logMAR.[6-12] One year later, 50% of patients receiving placebo lost ≥3 ETDRS lines—that is, 50% deteriorated to an average VA >1.0 logMAR. According to our model, 51.3% of patients would experience low vision (VA >1.0 logMAR) due to AMD and 47.2% would progress to blindness. The prognosis was 82.15 months with monocular vision and a further 49.40 months with bilateral VA >1.0 logMAR. Also at 1 year, 16.8% of patients with AMD would experience depression due to VA loss and 95 per 1000 would sustain a fractured hip related to visual impairment. Reduced life expectancy due
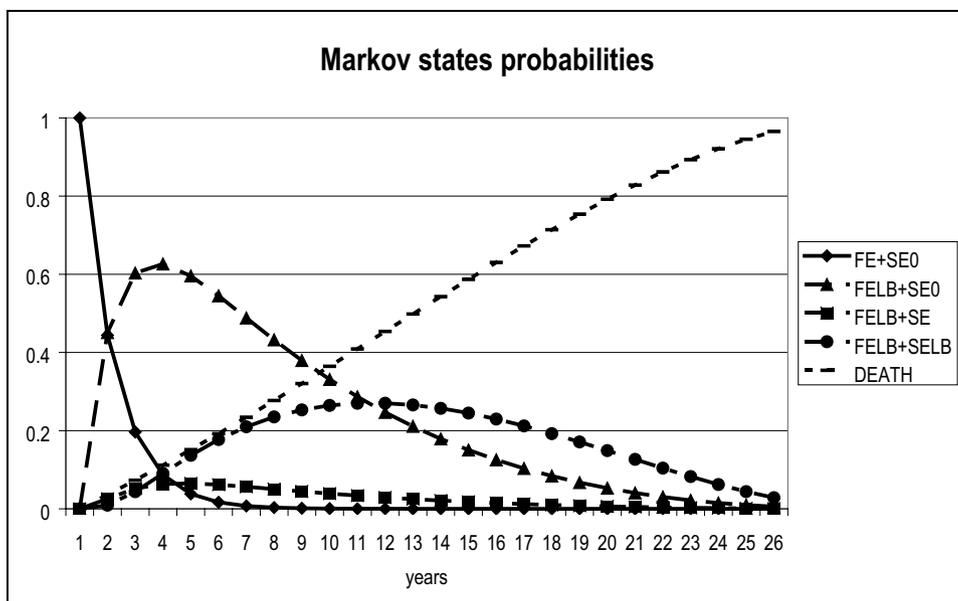
FIGURE 2. Markov state model probabilities as functions of time. Two Markov states are not measured (FE+SE; FE+SELB) since their probabilities never reached 0.05.

to blindness would be 26.24 months, and 1.6% of patients would require institutional care because of AMD.

When the probability of VA >1.0 logMAR developing in one eye was fixed at 70%, the prognosis was low vision at 1 year for 51% of patients and blindness for the remaining 49%. When the 1-year probability of development of VA >1.0 logMAR was set at 10%, the mean time with VA >1.0 logMAR was 62.64 months for the first eye affected by CNV. The mean time increased to 84.56 months when the 1 year probability of VA >1.0 logMAR was 70%. All parameters (blindness and low vision prevalence rates, depression, hip fracture, reduced life expectancy, and institutionalization) increased with the probability of VA >1.0 logMAR. The increase, however, followed a quadratic function and reached a plateau when the probability of VA >1.0 logMAR was equal or superior to 50%.

Table 3 illustrates the public health consequences of an effective AMD drug that would reduce the risk of VA >1.0 logMAR in decreasing steps from the initial level. Values of all disability parameters in Table 3 decreased in inverse proportion to the initial probability of VA >1.0 logMAR. Thus, a 20% reduction in the 1-year risk of monocular VA >1.0 logMAR, when the probability of the development of VA >1.0 logMAR was set at 70%, decreased the duration of monocular vision by only −2.41 months, but decreased it by −15.18 months when the probability was 30%. Corresponding results with the same levels of reduced risk extended from −3.8 to −23.06 months for blindness, from −9.65 per 1000 to −71.79 per 1000 for depression, from −4.32 per 1000 to −18.15 per 1000 for new hip fractures, and from −1.37 per 1000 to −4.87 per 1000 for institutionalization. Although further gains with these parame-

ters were small when the initial probability of VA >1.0 logMAR was high (70%), they became more important when the initial probability was low (30%).

Figure 3 shows the probabilities of developing low vision and blindness over 25 years as functions of four increasing annual probabilities (0.1, 0.3, 0.5, and 0.7) of VA >1.0 logMAR. The probability of low vision peaked at >0.75 when the annual probability of VA >1.0 logMAR was ≥0.3. Low vision reached a plateau probability of approximately 0.6 between 10 and 12 years after AMD onset when the annual probability of VA >1.0 logMAR was 0.1. The probability of blindness at 25 years increased to almost 0.8 when the annual probability of VA >1.0 logMAR was ≥0.3 and reached 0.6 for an annual probability of VA >1.0 logMAR equal to 0.1.

Table 4 shows further results that may be derived from our Markov model. The model extrapolated lifetime results from three published, randomized, well-controlled clinical trials of verteporfin, pegaptanib, and anecortave in AMD, all versus placebo.[8,12,43] The anecortave acetate sample was the smallest. No major age difference was reported at inclusion. The incidence rate of placebo failure was highest in the TAP trial. Clinical efficacy was greatest in the anecortave trial. The effect of treatment on the incidence rate of low vision was weak, according to our model. All other comorbidity and institutionalization incidence rates were less after active treatments than after placebo. Higher clinical efficacy was associated with greater decreases in comorbidity (anecortave versus verteporfin and pegaptanib trials). With the same level of clinical efficacy (verteporfin and pegaptanib trials), a higher placebo failure rate was accompanied by more comorbidity.

TABLE 2. Visual Impairment and Vision-Related Comorbidity According to the Probability of VA >1.0 logMAR at 1 Year

	10%	20%	30%	40%	50%	60%	70%
Probability of developing VA >1.0 logMAR at 1 year in an AMD eye							
Visual impairment status: total population							
Low vision due to AMD (% patients)	46.1	50.6	51.8	52.0	51.3	50.8	51.0
Blindness due to AMD (% patients)	22.7	37.3	43.9	45.8	47.2	47.5	49.0
One eye >1.0 logMAR due to AMD (mo)	62.64	73.51	77.82	80.38	82.15	83.49	84.56
Blindness due to AMD (mo)	18.52	33.49	41.58	46.33	49.40	51.57	53.20
Co-morbidities and institutionalization associated with visual impairment							
Depression prevalence rate associated with AMD (% patients)	8.3	13.2	15.5	16.5	16.8	17.0	17.8
Number of new hip fractures associated with AMD per 1000 patients	72.84	87.09	90.99	93.32	94.85	94.59	99.17
Loss of life expectancy associated with AMD (mo)	17.94	22.62	24.57	25.60	26.24	26.68	27.00
Institutionalization prevalence rate associated with AMD (% patients)	0.9	1.1	1.3	1.5	1.6	1.6	1.7

TABLE 3. Public Health Consequences of Reducing the Probability of VA >1.0 logMAR at 1 Year, as a Function of the Initial Probability

Probability of developing VA > 1.0 logMAR at 1 year in AMD eye (gain in effectiveness)	20%	30%	40%	50%	60%	70%
One eye >1.0 logMAR due to AMD (mo)						
−10%	−10.87	−4.31	−2.56	−1.77	−1.34	−1.07
−20%		−15.18	−6.87	−4.33	−3.11	−2.41
−30%			−17.74	−8.64	−5.67	−4.18
−40%				−19.51	−9.98	−6.74
Both eyes >1.0 logMAR due to AMD (mo)						
−10%	−14.97	−8.09	−4.75	−3.07	−2.17	−1.63
−20%		−23.06	−12.84	−7.82	−5.24	−3.8
−30%			−27.81	−15.91	−9.99	−6.87
−40%				−30.88	−18.08	−11.62
Depression per 1000 patients						
−10%	−48.25	−23.54	−9.65	−3.48	−1.93	−7.72
−20%		−71.79	−33.19	−13.13	−5.41	−9.65
−30%			−81.44	−36.67	−15.06	−13.13
−40%				−84.92	−38.6	−22.78
Number of new hip fractures associated with AMD per 1000 patients						
−10%	−14.25	−3.9	−2.33	−1.53	0.26	−4.58
−20%		−18.15	−6.23	−3.86	−1.27	−4.32
−30%			−20.48	−7.76	−3.6	−5.85
−40%				−22.01	−7.5	−8.18
Institutionalization per 1000 patients						
−10%	−2.58	−2.29	−1.62	−0.73	−0.16	−1.21
−20%		−4.87	−3.91	−2.35	−0.89	−1.37
−30%			−6.49	−4.64	−2.51	−2.1
−40%				−7.22	−4.8	−3.72
Life expectancy (mo)						
−10%	−4.68	−1.95	−1.03	−0.64	−0.44	−0.32
−20%		−6.63	−2.98	−1.67	−1.08	−0.76
−30%			−7.66	−3.62	−2.11	−1.4
−40%				−8.3	−4.06	−2.43

DISCUSSION

Clinical trial endpoints for neovascular AMD have become standardized in recent years after the TAP and VIP studies.[6–12] Patients in these studies were defined as clinically stable when best corrected VA deterioration was <3 lines on the ETDRS chart, according to a standard protocol. Study durations were 1 to 2 years, followed by open-label treatment. Trial inclusion and exclusion criteria differed with respect to lesion size, lesion description, and other patient and lesion characteristics.

From a public health viewpoint a decrease of VA could be regarded as an intermediate endpoint, preceding blindness. Primary endpoints are visual impairment and related comorbidity, since they represent outcomes for which health authorities would be willing to pay. However, according to our model primary visual impairment data would need to be collected for 10 to 12 years, until blindness prevalence reaches asymptote, which would be socially unacceptable. Market access to a drug could not be postponed for such a long period, simply to document the blindness rate. The delay would dramatically decrease the chances of elderly patients' benefiting from new treatments, which is why modeling is an appropriate way to provide decision makers with relevant information.

Our Markov model allowed us to estimate the impact of treatments on outcomes. Extrapolations from the results of published clinical trials were easy to conduct. VA was, on average, 0.7 logMAR for the treated eyes of patients in the PDT and pegaptanib clinical trials. Comparison to eyes that responded to treatment (VA loss <3 ETDRS lines), the average VA of nonresponding eyes was 1.0 logMAR. Thus, the failure rate reported by a clinical trial approximates the probability of blindness caused by AMD. Therefore, time to failure could be standardized on yearly probabilities (as in our calculations), by either exponential modeling or independent probabilistic calculations. Linear extrapolation could also be used to obtain more accurate results.

When extrapolating public health impact from the three available placebo-controlled, randomized clinical trials, effects on low vision prevalence rates were small (<1.0%) in all trials, because the selected patients had low VA (0.7 logMAR) at baseline. Reduction of the low-vision prevalence rate depends on early diagnosis *and* effective treatment, when VA is least impaired. Because the first condition (low VA at baseline) was not satisfied, the public health impact of all three effective treatments could not be estimated accurately. All morbidity parameters decreased in an appropriate manner and both visual function and the related comorbidities were controlled significantly. Anecortave acetate showed better results than its competitors, because it differed more from placebo. The reader should note that sample sizes were small in the anecortave trial,[43] so the results were associated with high variability. The verteporfin efficacy reported by TAP[6–10] was very close to that for pegaptanib reported by Gragoudas et al.,[12] with differences close to 15% compared with placebo. However, lesions in the TAP study were more aggressive than those in the pegaptanib trial, as evidenced by the placebo failure rates (54% and 45%, respectively).

The natural history of AMD lesions is critical to the impact they make on vision at the population level. The average age of patients when the first eye was diagnosed with AMD was 75 years in our model. The population life expectancy (modeled for Western developed countries) was sufficient for the disease to affect both eyes. This was especially true for lesions that develop rapidly. In the absence of effective treatments, the ageing of this population and increased life expectancy would reinforce the trend toward blindness.
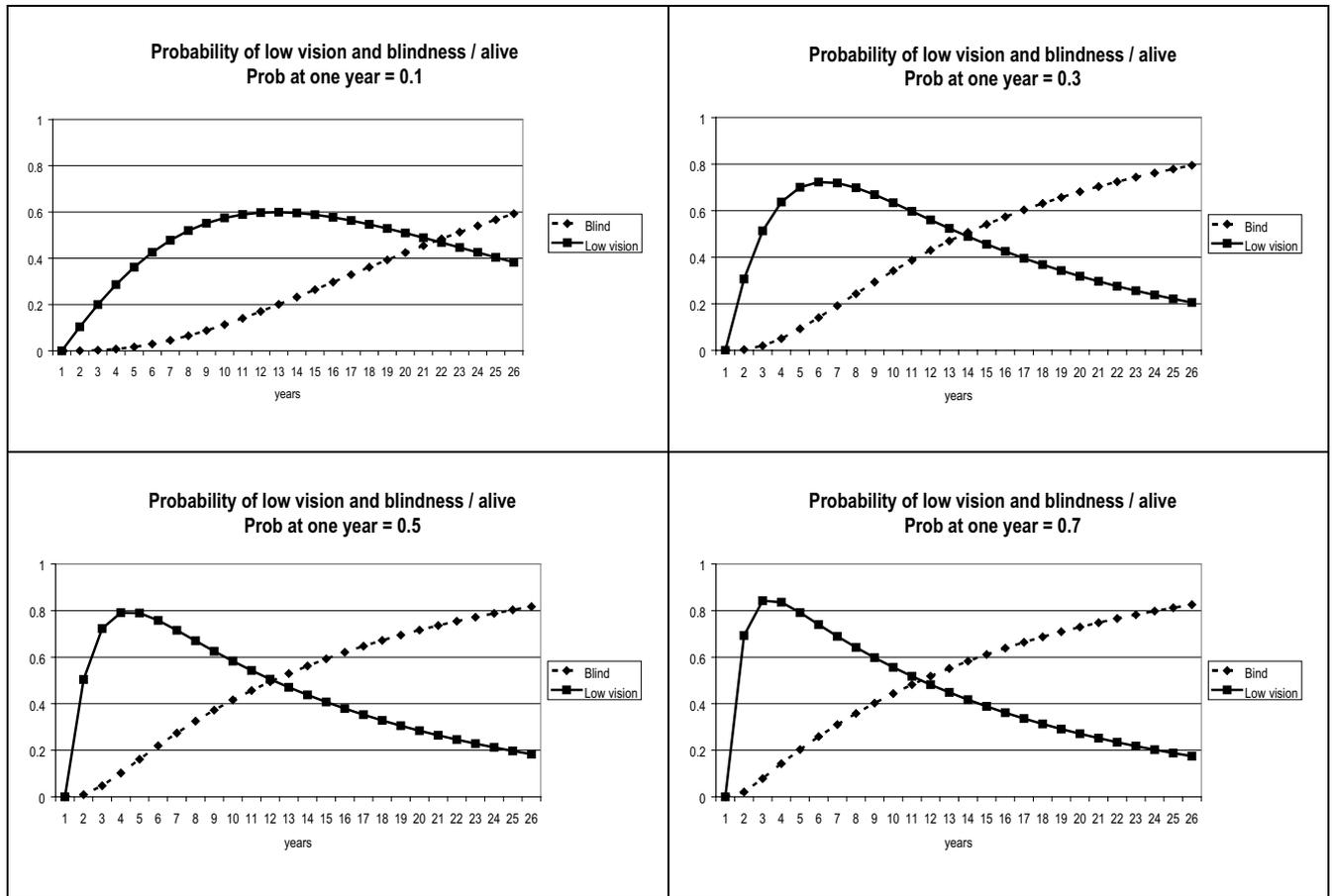
FIGURE 3. Probability of low vision or blindness according to four risk levels for VA >1.0 logMAR over 25 years.

TABLE 4. Public Health Impact Extrapolated from Verteporfin, Pegaptanib, and Anecortave Placebo-Controlled Trials

Chemical entity trial	Verteporfin TAP trial	Anecortave trial	Pegaptanib trial
Sample Size, *n*	Placebo 207 Verteporfin 402	Placebo 30 Anecortave 33	Placebo 296 Pegaptanib 294
Age (y)	75.3	77.0	76.4*
Failure rate at 1 year	Placebo 54%, Verteporfin 39%	Placebo 47%, Anecortave 21%	Placebo 45%, Pegaptanib 30%
Visual impairment status: all populations			
Low vision patients due to AMD (% patients)	0.9	−0.8	0.2
Blind patients due to AMD (% patients)	−1.7	−8.8	−2.6
One eye >1.0 logMAR due to AMD (mo)	−2.56	−7.68	−3.45
Blindness due to AMD (mo)	−4.41	−14.18	−6.29
Comorbidities and institutionalization associated with visual impairment			
Depression prevalence rate associated with AMD (% patients)	−0.5	−3.3	−1.2
Number of new hip fracture associated with AMD per 1000 patients	−1.66	−6.91	−3.10
Loss of life expectancy associated with AMD (mo)	−0.92	−3.23	−1.35
Institutionalization prevalence rate associated with AMD (% patients)	−0.1	−0.5	−0.3

* Weighted estimates: percentages applied to mid ranges. Results at 1 year were extrapolated over a patient's lifetime by using the Markov model. Incremental values (placebo-chemical entity) are reported. Negative values indicate superiority over placebo.

Our model made many assumptions, and some may be questioned in the future when results of AMD treatments are better documented. First, progression of the lesion and loss of VA in the second eye were assumed to be similar to effects in the diseased first eye. Second, the probability of AMD in the second eye was fixed at 30% for year 5. If this is too low, we have underestimated the consequences of blindness. Third, no age limit was set for patients to receive treatment. Fourth, drug efficacy was independent of age. Fifth, when both eyes were affected by AMD, patients (Table 4) were assigned 0.7 logMAR for both eyes at diagnosis, because separate data were not available for better and worse eye VA. Sixth, treatment efficacy was assumed to remain constant over time (no tachyphylaxis).

The effects of ageing on mortality was incorporated into our model, whereas ageing's effects on cardiovascular disease and other comorbidities, were not. As with the no tachyphylaxis hypothesis, our method may have underestimated the impact of AMD on the blindness incidence rate.

A key finding was the important role of AMD's natural progression, which indirectly influenced the placebo response rate depending on lesion type. According to our model, and from a public health viewpoint, an aggressive AMD lesion may be defined by a probability >50% of VA in the affected eye that reaches the threshold of 1.0 logMAR within 1 year. Also according to our model, the probability of blindness at 85 years was close to 45%, whereas the visual impairment prevalence rate in a similarly aged French population was 15%.[44] Such lesions need highly effective treatment, and possibly a combination of drugs, with supporting clinical evidence. Our model also assumed constant efficacy over time so as to reap the full benefit of treatment. Acute treatment tachyphylaxis would necessitate different maintenance therapy.

CONCLUSIONS

Further research is needed to confirm and refine our findings. The need is great for long-term efficacy data on AMD populations documenting blindness and low-vision prevalence rates. Evidence demonstrating the effectiveness, or ineffectiveness, of treatment combinations and maintenance therapy is also needed, so that patients with AMD can be offered adequate management options.

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