Cost-effectiveness of Vitamin Therapy for Age-Related Macular Degeneration

David B. Rein, PhD,[1] Jinan B. Saaddine, MD, MPH,[2] John S. Wittenborn, BS,[1] Kathleen E. Wirth, BA,[1] Thomas J. Hoerger, PhD,[1] K. M. Venkat Narayan, MD,[2] Traci Clemons, PhD,[3] Stephen W. Sorensen, PhD[2]

Objective: To determine the cost-effectiveness of vitamin therapy (antioxidants plus zinc) for all indicated patients diagnosed with age-related macular degeneration (AMD).

Design: We compared the impacts of vitamin therapy with those of no vitamin therapy using a computerized, stochastic, agent-based model. The model simulated the natural history of AMD and patterns of ophthalmic service use in the United States in a cohort from age 50 years until 100 or death.

Participants and/or Controls: The model created 20 million simulated individuals. These individuals each received both the intervention (vitamin therapy after diagnosis) and the control (no vitamin therapy). Expected outcomes generated when vitamins were taken after diagnosis were compared with the expected outcomes generated when they were not.

Methods: The model created individuals representative of patients in the U.S. Incidence of early AMD was based on published studies, as was vision loss and response to choroidal neovascularization therapies. Post–incident disease progression was governed by previously unpublished data drawn from the Age-Related Eye Disease Study.

Main Outcome Measures: Extent of disease progression, years and severity of visual impairment, cost of ophthalmic care and nursing home services, and quality-adjusted life years (QALYs). Costs and benefits were considered from the health care perspective and discounted using a 3% rate. The analysis was run for 50 years starting in 2003.

Results: Compared with no therapy, vitamin therapy yielded a cost-effectiveness ratio of $21 387 per QALY gained and lowered the percentage of patients with AMD who ever developed visual impairment in the better-seeing eye from 7.0% to 5.6%.

Conclusions: Our model demonstrates that vitamin therapy for AMD improves quality of life at a reasonable cost. *Ophthalmology 2007;114:1319–1326 © 2007 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is the leading cause of blindness and visual impairment among ≥65-year-olds in the United States and the industrialized world. Approximately 1.75 million Americans over age 50 are living with advanced vision-threatening AMD, and this number is expected to increase 50% to 2.95 million by 2020.[1] Recent evidence has found that AMD patients who take high-dose antioxidant plus zinc vitamin supplements* during the early stages of AMD are at a reduced risk of choroidal neovascularization and geographic atrophy (GA), the advanced vision-threatening symptoms of AMD.[2]

Although 2 studies[3,4] have evaluated the potential impact of vitamin supplements, neither has estimated the cost-effectiveness within the context of the U.S. health care system. The first, the Age-Related Eye Disease Study (AREDS),[3] estimated that as many as 300 000 cases of advanced AMD could be avoided in the U.S. over 5 years if all eligible patients took vitamin supplements containing antioxidants plus zinc; however, the study did not consider the economic impact. The second, Hopley et al,[4] did estimate the cost-effectiveness ratio (CER) of vitamins (approximately $31 800 [£18 948] in March 2003—per quality-adjusted life year [QALY]) but presented results only for patients 65 years and older, used data from Australia and Great Britain, and included the cost of diagnostic screening as part of the vitamin intervention.

This study is the first to assess the independent incremental cost-effectiveness of prescribing antioxidants plus zinc for cases of AMD diagnosed in the course of routine ophthalmic eye care compared with no use of vitamins for those same patients. We look at the impact for all patients older than 50 years with AMD using U.S. cost and preva-

Originally received: May 2, 2006.
Accepted: October 26, 2006. Manuscript no. 2006-502.

[1] RTI International, Research Triangle Park, North Carolina.

[2] Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

[3] Emmes Corp., Rockville, Maryland.

Funding for this research was provided by the Division of Diabetes Translation, Centers for Disease Control and Prevention (contract no. 200-2002-00776).

Correspondence and reprint requests to David B. Rein, PhD, RTI International, 2957 Flowers Road, Suite 119, Atlanta, GA 30341. E-mail: drein@rti.org.

*Age-Related Eye Disease Study antioxidant plus zinc vitamin supplements contained 500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of β-carotene, plus 80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide to prevent potential anemia.

ISSN 0161-6420/07/$–see front matter
doi:10.1016/j.ophtha.2006.10.041

lence data. As a result, this study can be used to provide cost-effectiveness information to inform normal ophthalmic practice for patients diagnosed with AMD in the U.S. This study also presents a new natural history model of AMD, based on the symptoms of large drusen and retinal pigment epithelium (RPE) abnormalities and driven by previously unpublished evidence from the AREDS.

Materials and Methods

We developed a stochastic agent-based model in which simulated individuals are created at age 50 years and observed until death or age 100. The model simulated 20 million discrete individuals who varied in terms of their demographic characteristics, longevity, and use of normal ophthalmologic care. Stochastic microsimulation models have been used in the past to evaluate the cost-effectiveness of interventions to treat diabetic retinopathy and retinopathy of prematurity.[5–7] All individuals in the model also could develop AMD, of course. The model tracked each patient's costs, incidence and subsequent progression of AMD (if any), visual impairment resulting from AMD, and patient QALYs lived. Visual impairment and blindness were determined based on the functionality of an individual's better-seeing eye, accounting for losses of acuity, and contrast sensitivity (CS). Patient quality of life decreased based on the extent of visual impairment. For each simulated person, the model tracked years of visual loss and blindness, QALYs, and ophthalmologic costs related to routine ophthalmologic care, AMD vitamin prophylaxis and medical treatment, and nursing home placement. For this analysis, we evaluated costs from the health care perspective and excluded such costs as the time of informal caregivers and lost productivity due to visual impairment. The AMD simulation is part of a larger Multiple Eye Disease Simulation model [Rein DB, Wittenborn JS, Wirth KE, et al. Developing a multiple eye disease simulation model (no. 28). Presented at: 3rd RTI Fellows Symposium, April 3–4, 2006, Chapel Hill, North Carolina] and is programmed in AnyLogic (XJ Technologies Co., Ltd., St. Petersburg, Russia).

Model Structure

Upon model initiation, the model simulated a certain percentage of patients with GA and choroidal neovascularization and early preadvanced AMD, based on the percentage of the population with these conditions at age 50 years.[1] The vast majority of patients were not assigned AMD at initiation and instead experienced an annual probability of incident AMD in subsequent years of the model. Patient AMD progression was evaluated based on a joint assessment of both eyes until the patient's first eye progresed to advanced AMD, after which the model simulated disease progression in each eye independently.

Our conceptual model of AMD and the probabilities of patient progression from one stage to another were based on previously unpublished data obtained from the AREDS.[8] Groups of patient symptoms were categorized into discrete states with the same probability of progression to advanced AMD (GA or choroidal neovascularization) in the AREDS data. In the AREDS, progression to advanced AMD was best predicted based on a joint assessment of both eyes of the patient. Consequently, in our model patient disease states were based on the presence or absence of large drusen (>125 μm) or RPE abnormalities in one or both eyes. Patients with early and intermediate AMD were categorized into mutually exclusive states numbered 0 to 4. State 0 patients had no large drusen or RPE abnormalities in either eye; state 1 patients had either large drusen in one eye or RPE abnormalities in one eye, with no other symptoms; state 2 patients had large drusen in both eyes, with no RPE abnormalities, RPE abnormalities in both eyes with no large drusen, or large drusen and RPE abnormalities in one eye each; state 3 patients had large drusen in both eyes, with RPE abnormalities in one eye, or RPE abnormalities in both eyes with large drusen in one eye; and state 4 patients had large drusen and RPE abnormalities in both eyes (Table 1).

Table 1. Risk States for the Development of Advanced Age-Related Macular Degeneration (AMD) in the First Eye Based on the Large Drusen and Pigment Abnormality Status of Both Eyes

	Eyes with Pigment Abnormalities		
Eyes with Large Drusen	*Neither*	*One*	*Both*
Neither	0	1	2
One	1	2	3
Both	2	3	4

Patients in states 1 through 4 had an estimated yearly probability of moving to any other state, including the advanced AMD states of GA and choroidal neovascularization (Fig 1). Contrary to popular perceptions of AMD, AREDS patients were observed moving forward and backward among all preadvanced AMD states. Our model incorporated both forward and backward transitions (backward transitions not shown in Fig 1). Eyes with GA also could develop choroidal neovascularization, whereas eyes that developed choroidal neovascularization remained there until a patient's death.[9,10] Based on its proximity to the fovea, choroidal neovascularization was classified as extrafoveal, juxtafoveal, or subfoveal, with treatment options and the annual probability of visual loss depending on type.[11]

Loss of visual function occurred only from advanced AMD. Eyes with GA or choroidal neovascularization had an annual probability of losing 0.3 or 0.6 log units of acuity[2,12,13] and 0.3 or 0.75 log units of CS, which could be mediated by treatment.[12] At the end of each year, based on the worse impairment level of acuity or CS, eyes were categorized into 1 of 6 impairment categories: none, mild, moderate, U.S.-defined blindness, World Health Organization–defined blindness, and severe blindness based on the best-corrected visual function of the better-seeing eye.[14]

Progression Parameters, Care and Costs of Complications, and Health Utilities

Age-related macular degeneration prevalence at model initiation (age 50 years) was based on a meta-analysis of population-based study data.[1] Subsequent incidence of AMD (movement from state 0 to state 1 or higher) was set according to age using incidence estimates obtained from population-based studies.[15–19] Transitions among states 1 through 4 and from those states to GA and choroidal neovascularization were based on a data matrix of transition probabilities estimated by the AREDS group.[20] All patients diagnosed with AMD were assumed to have received medical treatment and services recommended by the American Academy of Ophthalmology's preferred practice patterns.[11] For example, all patients with extrafoveal or juxtafoveal choroidal neovascularization received photocoagulation or focal laser surgery. Costs for these services were assigned based on the Centers for Medicare & Medicaid Services fee schedule.[20,21] Because patients with visual impairment and blindness are at an elevated risk of using nursing home services,[22] the model also tracked the use and costs of nursing home services.[23]

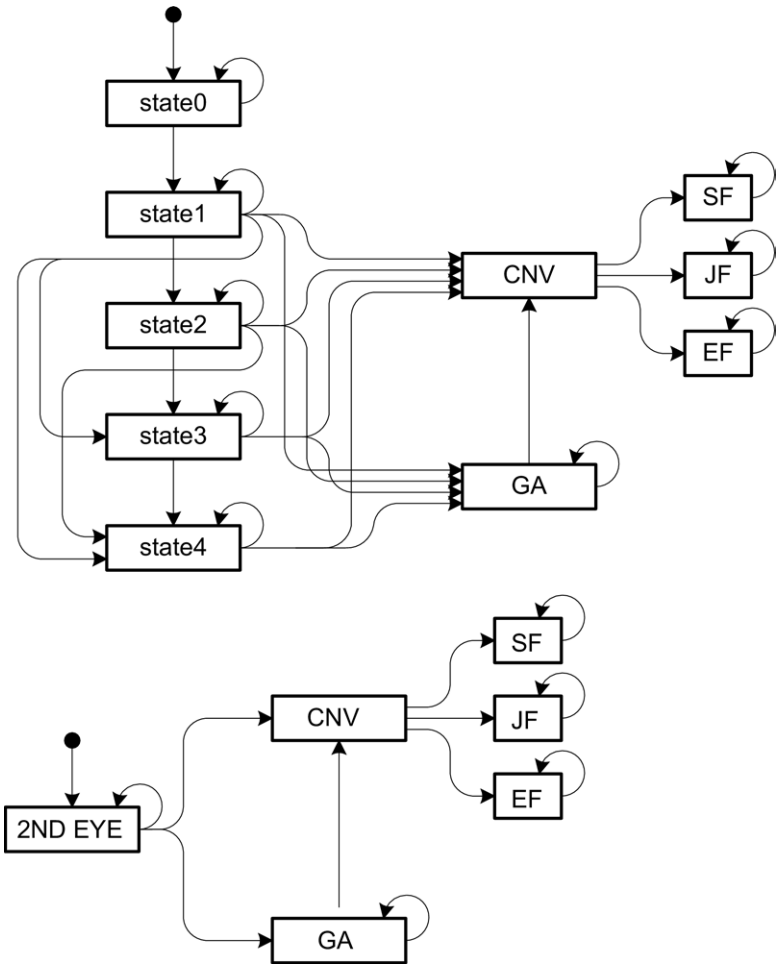

Figure 1. Natural history of age-related macular degeneration shown in disease states (boxes) and possible transitions between states (lines) for a patient's first eye and second eye (backward transitions not shown). CNV = choroidal neovascularization; EF = extrafoveal; GA = geographic atrophy; JF = juxtafoveal; SF = subfoveal.

Patient QALYs were calculated annually by multiplying the value of 1 minus patients' visual impairment–related health utility decrement (if any) by a uniform background utility of 0.87 (the average health utility of people at age 50 years). Annual health utilities were discounted to the base year and summed for all years of life. Health utility decrements were based on published studies of QALY decrements associated with visual impairment calculated using a time-tradeoff approach.[24]

Normal Use of Ophthalmic Services

Based on a National Center for Health Statistics–suggested methodology,[25] we used the 2002 National Ambulatory Medical Care Survey data[26] to identify the annual number of patients with any ophthalmologist visit and assumed that a diagnostic screen for AMD (slit-lamp biomicroscopy) would occur at all visits for patients in this age range. Our resulting estimated rates of service use were similar to those found in other studies.[27]

Calibration and Validation

To calibrate the model, we compared its results to the proportion of patients with intermediate AMD (states 1–4), advanced AMD (GA and choroidal neovascularization), visual impairment, and blindness reported by a National Eye Institute (NEI)–sponsored meta-analysis of population-based epidemiological studies.[1] We then altered the model's age-specific transition probabilities from state 0 to state 1 (incidence of AMD) within the range of possible values reported in the literature while holding all other transition probabilities constant until our model resulted in the best fit of the NEI data. Because the model underpredicted cases of GA, we increased all transitions to GA in the model by 10%. This adjustment still resulted in an underprediction of GA relative to the NEI data, but one that was less extreme than first observed.[20]

We then validated the model according to recommended standards outlined by the International Society for Pharmacoeconomics and Outcomes Research Task Force.[28] Internal testing was conducted by altering parameters to extreme values and assessing the impact on results. A degree of external validation was gained through our calibration of results against the NEI data because our model generates prevalence values similar to those of the NEI study after calibrating only the parameters governing progression from state 0 to state 1 and subsequent progressions from states 1 through 4 to GA.

Interventions

We evaluated the impact of treating all patients diagnosed with AMD in either eye in states 1 through 4 with antioxidant plus zinc

vitamin supplements as recommended by the AREDS research group.[2] The AREDS identified a 25% risk reduction of disease progression among patients taking vitamin supplements, compared with those taking a placebo. In our intervention scenario, patients diagnosed with AMD received vitamin therapy, with the effect of reducing their annual forward transition probabilities from states 1 through 4 by 25%. Vitamin therapy was assumed to have no impact on backward transitions or transitions from GA to choroidal neovascularization.

Cost-effectiveness Analysis and Other Outcomes

We report the costs of vision-related medical care, vision-related nursing home placements, and total costs. Vision-related medical care includes the cost of the normal use of ophthalmic services, cost of additional ophthalmologic services needed to monitor AMD after a diagnosis, cost of vitamin therapy for AMD, and costs of laser therapy and photodynamic therapy to treat choroidal neovascularization. Vision-related nursing home costs include the incremental nursing home placements attributable to visual impairment and blindness. We also report the percentage of AMD patients who ever entered AMD states 2, 3, and 4 (all incident AMD patients are assumed to enter state 1), percentage of AMD patients with choroidal neovascularization or GA in either eye, percentage of AMD patients who had visual impairment or blindness in at least one eye, and percentage of AMD patients who had visual impairment or blindness in the better-seeing eye.

One-Way Sensitivity Analysis

To test the sensitivity of the model to uncertain parameters, we increased and decreased the risk-reduction benefit of vitamins by 10 percentage points (15%–35%) and doubled and nearly halved the cost of vitamins. The base vitamin costs were based on the average prices observed in a survey of online and retail prices and redbook average wholesale prices for each vitamin component. Recently, a branded single daily pill vitamin meeting the AREDS dosing recommendations was marketed at a price similar to or higher than our baseline price. Doubling the cost of vitamins reflects the higher price of daily vitamin supplements targeting AMD and also may capture additional unobserved costs of any rare adverse complications of intensive vitamin therapy. The lower vitamin price was calculated based on the minimum observed vitamin price ($59.06), slightly over half the baseline cost. We varied the probability of developing GA and choroidal neovascularization by adjusting all transitions in the model to GA and choroidal neovascularization upward and downward by 25% and considered the cost-effectiveness of vitamins when long-term care costs were excluded. We also varied the discount rate from 0% to 5%. We report full results for the discount rate and risk reduction associated with vitamins. For other variables, we report only the result that could challenge the conclusion of the model's point estimate.

Results

Vitamin therapy offered to all patients diagnosed with AMD in states 1 through 4 led to an undiscounted decrease of 0.036 years of visual loss per person in the model and an increase of discounted QALYs of 0.004. When considering only those with AMD, as opposed to the entire population, visual loss per person decreased by 0.095 years and QALYs increased by 0.011. Including the cost of vitamins, treatment costs per person in the sample increased from $583 to $721, whereas per-person nursing home costs decreased from $266 to $217. Total costs, compared with no vitamin therapy, increased by $88 per person. The CER was $21 387 per QALY gained (Table 2). Relative to no vitamin therapy, the percentage of patients with AMD who ever developed GA in either eye dropped from 10.1% to 8.1%, and the percentage who ever developed choroidal neovascularization in either eye dropped from 16.0% to 13.0%. The percentage of patients with AMD who ever developed visual impairment or blindness in either eye dropped from 21.4% to 17.4%, and the percentage who ever developed visual impairment or blindness in the better-seeing eye dropped from 7.0% to 5.8% (Fig 2).

Sensitivity Analysis

Exclusion of long-term care costs had a relatively minor impact on the cost-effectiveness of vitamin therapy. Decreasing the risk-reduction benefit of vitamin therapy to 15% and decreasing the baseline probability of developing GA and/or choroidal neovascularization by 25% had a moderate impact on the cost-effectiveness of vitamin therapy. Changes in the discount rate and cost of vitamins had a more dramatic impact on results (Fig 3). Excluding nursing home costs increased the CER to $33 250. Decreasing the impact of vitamins increased the CER to $47 351. Similarly, decreasing the probability of GA and choroidal neovascularization by 25% increased CERs to $43 424 and $47 085 per QALY, respectively. Changing the annual cost of vitamins had the most substantial impact. Doubling vitamin costs from $114.23 to $228.46 increased discounted costs per person by $279 (with no corresponding increase in QALYs), resulting in a CER of $61 683. Using the minimum observed prices for vitamins resulted in a slightly cost-saving CER of −$865.

Discussion

Vitamin therapy improves visual outcomes by delaying or preventing the onset of advanced AMD while also increasing health care costs. The cost-effectiveness of vitamin therapy ($21 387/QALY) compares favorably with other interventions and treatments to prevent AMD-related visual impairment and blindness. For example, laser photocoagulation therapy for extrafoveal choroidal neovascularization

Table 2. Incremental Cost-Effectiveness by Intervention

	Cost			Years of Visual Impairment and Blindness	QALYs	Incremental Cost-effectiveness Ratio (Total Cost/QALY)
	AMD	*Nursing Home*	*Total*			
Conventional treatment	$583.41	$265.55	$848.96	0.26049	15.6221	
Vitamin therapy for all diagnosed	$720.87	$216.51	$937.38	0.22501	15.6263	
Incremental	$137.46	−$40.94	$88.42	−0.0355	0.004	$21 887

AMD = age-related macular degeneration; QALY = quality-adjusted life years.

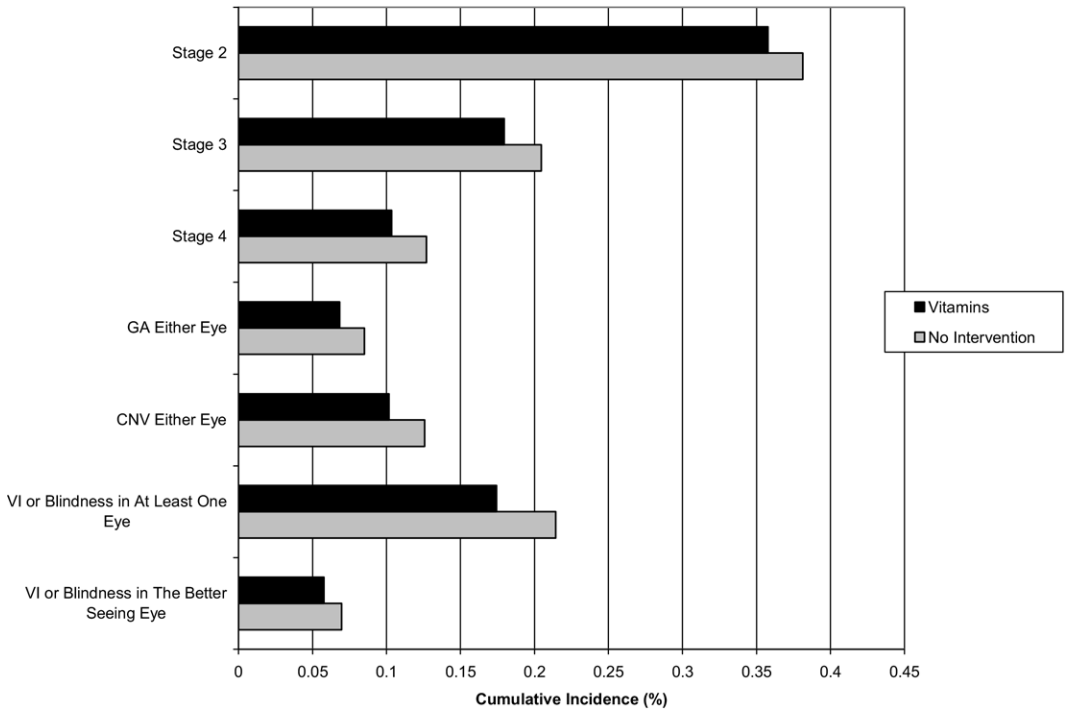

Figure 2. Cumulative incidence of age-related macular degeneration (AMD) states and complications among those with AMD (i.e., those who ever reached AMD state 1). CNV = choroidal neovascularization; GA = geographic atrophy; VI = visual impairment.

was found to have a CER of $24 720 per QALY (2004 dollars),[29] similar to our finding for vitamins. The cost-effectiveness of photodynamic therapy with verteporfin to treat subfoveal choroidal neovascularization was estimated at $92 499 (2004 dollars) per QALY in the U.S.[30] and, more recently, at approximately $70 000 per QALY in Great Britain.[31] Vitamin therapy for AMD appears to be a reasonable investment of health resources compared with other

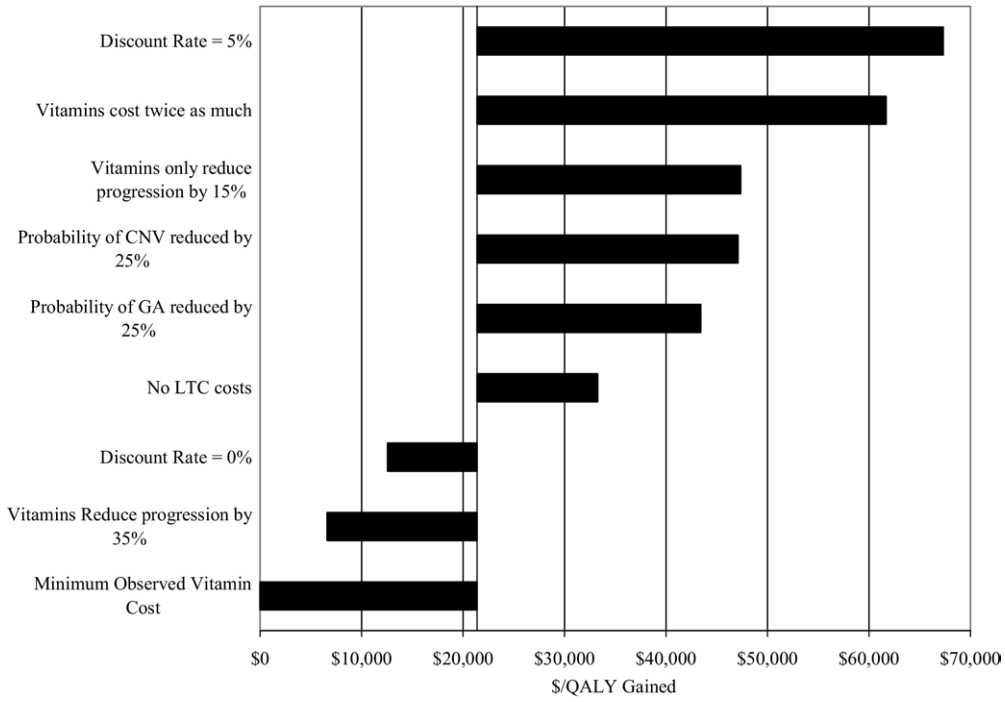

Figure 3. Sensitivity of cost-effectiveness ratio to changes in major model assumptions. CNV = choroidal neovascularization; GA = geographic atrophy; LTC = long-term care; QALY = quality-adjusted life year.

interventions, although there is no consensus regarding what constitutes an acceptable CER other than a cost-saving intervention.[32]

Vitamin therapy also compared favorably to many public health preventive services using the comparative methodology employed by the National Commission on Prevention Priorities.[33] Assuming a compliance rate among those prescribed above 85%, vitamin therapy for patients diagnosed with early and intermediate AMD would be considered as high a priority as breast cancer screening for women older than 50 years, *Chlamydia* screening for sexually active women younger than 25, calcium chemoprophylaxis for adolescent and adult women to prevent fractures, and vision screening for children to detect amblyopia, strabismus, and defects in visual acuity (VA).[33] Even at compliance rates as low as 30%, vitamin therapy is as desirable as the use of folic acid to prevent birth defects and routine screening for obesity with behavioral interventions for obese patients.[33]

At both compliance levels, vitamin therapy is more favorable than several other interventions such as screenings for depression, hearing, cholesterol risk, osteoporosis, or diabetes or counseling to prevent injury. Vitamin therapy is not as favorable as some low-cost high-benefit interventions such as screening for VA defects among adults older than 65 years or aspirin chemoprophylaxis to prevent cardiovascular events. However, the marginal impact of promoting the policy may be quite large even in comparison with these interventions, because the percentage of those diagnosed with early or intermediate AMD who are prescribed and use vitamins may be well below 50%. A study of eligible Australian AMD patients found that 53% of participants were aware of the availability of a vitamin formula to prevent advanced AMD, 38% were taking the supplement, and only 1% were taking the correct dose.[34] The level of knowledge of and compliance with vitamin therapy in the U.S. is unknown, but if it is similar to Australian levels, then promoting vitamin therapy for patients diagnosed would qualify as a top prevention priority (tied for sixth highest) by the National Commission on Prevention Priorities.

Our model's results were most sensitive to estimates of the discount rate and price of vitamin therapy. Sensitivity to the discount rate is a result of many of the benefits of vitamin therapy being realized at late ages. We observed a cost-neutral to cost-saving CER using the minimum observed market prices for vitamins. However, it is very unlikely that consumers could obtain this price, and in fact, they may be more likely to purchase single-pill AMD supplements that typically cost as much as or more than the average observed price used in the analysis. Our model also assumed no direct effect of vitamin therapy on backward transitions (improvements in symptoms). If vitamins lead to improvements in symptoms as well as simply slow forward progression, their cost-effectiveness would be even better.

After adjusting for differences in the definition of AMD, our model[35] adequately replicates the prevalence of AMD reported in the NEI meta-analysis.[1] The model also closely reproduces the combined prevalence of advanced AMD, although it does so by somewhat overpredicting choroidal neovascularization and underpredicting GA.

Several therapies, excluded from our model, are or will shortly be available to treat AMD-related choroidal neovascularization. Drugs to treat vascular endothelial growth factor, such as pegabtanib sodium injections and ranibizumab, have demonstrated effectiveness as treatments for choroidal neovascularization.[36] Other possible choroidal neovascularization treatments include corticosteroids with antiangiogenic properties and juxtasclerally administered intravitreal triamcinolone and anecortave.[36] These technologies may become integrated into the treatment of choroidal neovascularization, likely resulting in better long-term visual outcomes but possibly at substantially increased costs. Future research should evaluate the cost-effectiveness of these treatments relative to existing treatments and incorporate these results into models such as ours that evaluate the cost-effectiveness of prophylactic treatments given to those diagnosed with early and intermediate disease.

Our study finds a CER similar to that found by its closest counterpart ($31 800),[4] despite several key differences between the 2 studies. These differences include the fact that the former study considered the joint benefits of vitamins and screening; reported results only for those older than 65 years, whereas this study supports the use of vitamins for all patients 50 and over; used Australian epidemiological, medical cost, and life expectancy data; assumed no screening occurred in the absence of the intervention; and did not include the cost of nursing home care. The similarity of our results, despite these differences, adds evidence supporting vitamin therapy as a cost-effective treatment for AMD. Of note, this study evaluated the cost-effectiveness of treating only those patients diagnosed during the course of routine ophthalmic care. The incremental cost-effectiveness of adding additional screening to hasten diagnosis is likely to be less favorable. However, any such screenings also might identify other ocular disorders, thus increasing their overall potential benefit.

Limitations

This research is limited by several assumptions. First, our model considers cost from the health care perspective and does not include such costs as time of informal caregivers, hired home assistance workers, social assistance payments, rehabilitative equipment and training, and lost productivity due to visual impairment (although some economists argue that productivity losses are incorporated within the QALY value).[32] Second, all patients in our model diagnosed with advanced AMD receive guideline-recommended standards of care,[11] which likely results in increased and timelier laser therapy and photodynamic therapy for choroidal neovascularization than actual real-world treatment. If real-world patients actually receive suboptimal laser therapy and photodynamic therapy, then episodes of choroidal neovascularization will result in greater levels of visual impairment, associated greater QALY losses, but lower medical costs than those observed in our model. Third, we have assumed that the risk reductions currently observed only over the duration of the AREDS trial would continue for as many years as a patient took vitamins. If the effectiveness of vitamins wanes over time, the cost-effectiveness of their use would be less favorable. Fourth, our model tested the effec-

tiveness of the vitamin combination suggested by the AREDS.[3] Emerging evidence suggests that intake of lutein and zeaxanthin in addition to the AREDS supplement also may further inhibit the progression to advanced AMD.[37]

Despite these limitations, our model is the only simulation model of AMD that has been calibrated against external U.S. prevalence data, uses U.S. practice patterns and costs, incorporates losses of CS as well as acuity, and makes use of the most recent AREDS data on AMD progression. The limitations and assumptions embedded in this analysis were chosen to derive the most informative results, given limitations in knowledge, while focusing the risk of parameter uncertainty toward a conservative conclusion.

Implications

Our model demonstrates that vitamin therapy compares favorably with other medical therapies to prevent visual impairment from AMD and to improve health more generally. Readers should be aware that antioxidant formulations used in the AREDS contain β-carotene and therefore should never be recommended to patients who smoke.[38,39]* Our results support the use of vitamin therapy for all indicated patients diagnosed with AMD and 50 years or older.

Acknowledgments. The authors acknowledge Frederick L. Ferris III for allowing access to the AREDS data and providing key conceptual input in the development of the natural history model of AMD.

References

1. Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–72.
2. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417–36.
3. Age-Related Eye Disease Study Research Group. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. Arch Ophthalmol 2003;121:1621–4.
4. Hopley C, Salkeld G, Wang JJ, Mitchell P. Cost utility of screening and treatment for early age related macular degeneration with zinc and antioxidants. Br J Ophthalmol 2004;88:450–4.
5. Javitt JC, Canner JK, Sommer A. Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. Ophthalmology 1989;96:255–64.
6. Javitt JC, Dei Cas R, Chiang YP. Cost-effectiveness of screening and cryotherapy for threshold retinopathy of prematurity. Pediatrics 1993;91:859–66.
7. Eastman RC, Silverman R, Harris M, et al. Lessening the burden of diabetes: intervention strategies. Diabetes Care 1993;16:1095–102.
8. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. Control Clin Trials 1999;20:573–600.
9. van Leeuwen R, Klaver CC, Vingerling JR, et al. The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam Study. Arch Ophthalmol 2003;121:519–26.
10. Sunness JS, Gonzalez-Baron J, Bressler NM, et al. The development of choroidal neovascularization in eyes with the geographic atrophy form of age-related macular degeneration. Ophthalmology 1999;106:910–9.
11. American Academy of Ophthalmology Retina Panel. Preferred practice pattern. Age-related macular degeneration. San Francisco: American Academy of Ophthalmology; 2005:13–7. Available at: http://www.aao.org/education/library/ppp/upload/Age-Related_Macular_Degeneration.pdf. Accessed September 27, 2006.
12. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization—Verteporfin in Photodynamic Therapy report 2. Am J Ophthalmol 2001;131:541–60.
13. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy: five-year results from randomized clinical trials. Arch Ophthalmol 1991;109:1109–14.
14. Lennie P, Van Hemel SB, eds. Visual impairments: determining eligibility for social security benefits. Washington: National Academy Press; 2002:111–8. Available at: http://www.nap.edu/catalog/10320.html. Accessed September 27, 2006.
15. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. Ophthalmology 2002;109:1092–7.
16. Rubin GS, Bressler NM, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Effects of verteporfin therapy on contrast sensitivity: results from the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation—TAP report no. 4. Retina 2002;22:536–44.
17. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—TAP report 2. Arch Ophthalmol 2001;119:198–207.
18. Macular Photocoagulation Study Group. Laser photocoagulation for juxtafoveal choroidal neovascularization: five-year results from randomized clinical trials. Arch Ophthalmol 1994;112:500–9.
19. Klein R, Klein BEK, Tomany SC, et al. Ten-year incidence and progression of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 2002;109:1767–79.
20. Rein DB, Saaddine JB, Wittenborn JS, et al. Technical appendix: cost-effectiveness of vitamin therapy for age-related macular degeneration. Ophthalmology 2007;114:e13–20.
21. Centers for Medicare & Medicaid Services. Durable medical equipment, prosthetics/orthotics, and supplies fee schedules (d04_jan.zip). Available at: http://www.cms.hhs.gov/DMEPOSFeeSched/LSDMEPOSFEE/list.asp. Accessed September 27, 2006.
22. Wang JJ, Mitchell P, Cumming RG, et al. Visual impairment and nursing home placement in older Australians: the Blue Mountains Eye Study. Ophthalmic Epidemiol 2003;10:3–13.
23. Cooney JP Jr, Landers GM, Bae JP, Rein DB. Comparative assessment of cost and care outcomes among Georgia's community-based and facility-based long-term care programs. Atlanta: Georgia Department of Community Health; 2004:42–50.
24. Brown MM, Brown GC, Sharma S, Landy J. Health care

*Approximately 24% of Americans ages 45 to 64 years and 10% of American 65 and older smoke cigarettes.[40]

economic analyses and value-based medicine. Surv Ophthalmol 2003;48:204–23.
25. Burt CW. Using past visit information to enhance analysis of National Ambulatory Medical Care Survey (NAMCS) data. 2004. Available at: http://www.cdc.gov/nchs/data/ahcd/past%20vis%20duc%20handout%202004.pdf. Accessed September 27, 2006.
26. National Center for Health Statistics. National Ambulatory Medical Care Survey NAMCS02.exe, readme02.txt. Availableat:ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NAMCS. Accessed September 27, 2006.
27. Lee PP, Feldman ZW, Osterman J, et al. Longitudinal rates of annual eye examinations of persons with diabetes and chronic eye diseases. Ophthalmology 2003;110:1952–9.
28. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling Studies. Value Health 2003;6:9–17.
29. Busbee BG, Brown MM, Brown GC, Sharma S. CME review: A cost-utility analysis of laser photocoagulation for extrafoveal choroidal neovascularization. Retina 2003;23:279–87.
30. Sharma S, Brown GC, Brown MM, et al. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 2001;108:2051–9.
31. Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age-related macular degeneration: the UK case. Br J Ophthalmol 2004;88:1107–12.
32. Gold MR, Seigal JE, Russell LB, Weinstein MC, eds. Cost-effectiveness in Health and Medicine. Oxford, United Kingdom: Oxford University Press; 1996:3–21, 82–124.
33. Maciosek MV, Coffield AB, Edwards NM, et al. Priorities among effective clinical preventive services: results of a systematic review and analysis. Am J Prev Med 2006;31:52–61.
34. Ng WT, Goggin M. Awareness of and compliance with recommended dietary supplement among age-related macular degeneration patients. Clin Experiment Ophthalmol 2006;34:9–14.
35. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477–85.
36. Eter N, Krohne TU, Holtz FG. New pharmacological approaches to therapy for age-related macular degeneration. BioDrugs 2006;20:167–79.
37. Mitchell P, Smith W, Cumming RG, et al. Nutritional factors in the development of age-related eye diseases. Asia Pac J Clin Nutr 2003;12(suppl):S5.
38. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150–5.
39. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35.
40. Cigarette smoking among adults—United States, 2003. MMWR Morb Mortal Wkly Rep 2005;54:509–13. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5420a3.htm. Accessed September 27, 2006.