The cost effectiveness of age-related macular degeneration study supplements in the UK: Combined trial and real world outcomes data

Lee AY,[1] Butt T,[2] Chew E,[3] Agron E,[4] Clemons T,[5] Egan C,[2,6] Lee CS,[1] Tufail A,[2,6] on behalf of the UK EMR AMD Research Group.

1 University of Washington, Department of Ophthalmology, Seattle, WA, USA
2 Institute of Ophthalmology, University College London, London, UK
3 Division of Epidemiology and Clinical Research, National Institutes of Health, Bethesda, Maryland,USA.
4 National Eye Institute, Bethesda, Maryland,USA.
5 EMMES Corp, Rockville, Maryland, USA.
6 Moorfields Eye Hospital, London, UK

UK EMR AMD Research Group - Toks Akerele, Richard Antcliff, Stewart Armstrong, Clare Bailey, Catey Bunce, Usha Chakravarthy, Louise Downey, Robert L Johnston, Rehna Khan, Vineeth Kumar, Kaveri Mandal, Martin McKibbin, Salim Natha, Dawn Sim, Marie Tsaloumas, Atul Varma, Wen Xing

Correspondence to Adnan Tufail
Moorfields Eye Hospital NHS Trust, 162 City Road, London SE1 4TT
Adnan.Tufail@moorfields. nhs.uk

Funding
The health economic work was supported by a Macular Society grant.
The data used in this analysis from the AREDS study was supported by the intramural program funds and contracts from the National Eye Institute/National Institutes of Health (NEI/NIH), Department of Health and Human Services, Bethesda, MD. Contract No. HHS-N-260-2005-00007-C. ADB Contract No. N01-EY-5-0007.
Dr C. Lee was supported by NEI K23EY024921.
Drs. Lee were supported by Research to Prevent Blindness.
Dr Egan & Tufail received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology.
The collection of UK AMD EMR data used in the analysis was supported in part by unrestricted research award by Novartis Pharmaceuticals.

Acknowledgements
The Age-Related Eye Disease Study (AREDS) Research Group
UK EMR AMD Research Group

Keywords
Age-related macular degeneration, Supplements, Cost-effectiveness, Health economics

Competing Interests Statement: None of the authors have any personal financial interest in AREDS or other nutritional supplement products. Dr Tufail is a consultant for Allergan, Bayer, Chengdu Kanghong Biotech, Novartis, Roche.

Contributorship Statement: AYL,TB ,CE, EA,TC,EC,CSL and AT participated in study codesigning, data-analysis and evidence synthesis, and revising the manuscript. AYL, TB , AT also drafted the manuscript. THE UK EMR AMD Research Group TA,RA,SA,CB.CB.UC.LD.RL.RK,VK,KM,MM,SN,DS,MT,AV and WX participated in study data collection, evidence synthesis and revising the manuscript on previous UK EMR AMD data publications that fed the health economic model used.

Synopsis (35 words)
AREDS supplements are a dominant cost-effective intervention for category 4 AREDS patients, as they are both less expensive than standard care and more effective and therefore should be considered for public funding.

ABSTRACT (249 words)
Aims: To evaluate the cost-effectiveness of Age-Related Eye Disease Study(AREDS) 1 & 2 supplements in patients with either bilateral intermediate age-related macular degeneration, AREDS category 3, or unilateral neovascular AMD (nAMD), AREDS category 4.
Methods: A patient-level health state transition model based on levels of visual acuity in the better seeing eye was constructed to simulate the costs and consequences of patients taking AREDS vitamin supplements. Setting: UK National Health Service (NHS). The model was populated with data from AREDS and real-world outcomes and resource use from a prospective multicentre national nAMD database study containing 92 976 ranibizumab treatment episodes.
Interventions: Two treatment approaches were compared: immediate intervention with AREDS supplements or no supplements. Main outcome measures: Quality-adjusted life years (QALYs) and health care costs were accrued for each strategy, and incremental costs and QALYs were calculated for the lifetime of the patient. One-way and probabilistic sensitivity analyses were employed to test the uncertainty of the model.
Results: For AREDS category 3, the incremental cost-effectiveness ratio was £30,197. For AREDS category 4 compared to no intervention, AREDS supplements are more effective (10.59 vs 10.43 QALYs) and less costly (£52,074 vs 54,900) over the lifetime of the patient.
Conclusions: The recommendation to publicly fund AREDS supplements to category 3 patients would depend on the health care system willingness to pay. In contrast initiating AREDS supplements in AREDS category 4 patients is both cost saving and more effective than no supplement use and should therefore be considered in public health policy.

Introduction

Despite the introduction of anti-vascular endothelial growth factor (anti-VEGF) agents for the treatment of neovascular form of age-related macular degeneration (AMD), AMD remains the leading cause of blindness and visual impairment in the western world and is expected to increase in incidence with an aging population.[1] Delivery of anti-VEGF agents is burdensome and invasive for patients while costly, but is still associated with eventual visual reduction in many cases.[2] Intravitreal injection of anti-VEGF drugs, ranibizumab and aflibercept, is an established therapy to treat neovascular AMD (nAMD) in the UK National Health Service (NHS). In the UK, the National Institute of Health and Care Excellence (NICE) recommended the use of ranibizumab in August 2008,[3]] leading to almost exclusive usage of ranibizumab for nAMD in the UK NHS until the additional recommendation of aflibercept in 2013. [4] In clinical trials, aflibercept was shown to be non-inferior to ranibizumab,[5] and in clinical practice, outcomes of both drugs are similar if given in a similar dosing schedule.[6]

Given the burden and cost of treatment, prevention of nAMD seems therefore an attractive strategy to avoid the chronic and costly anti-VEGF therapies and preserve visual function. The Age-Related Eye Disease Study (AREDS) demonstrated that AMD patients who have at least one eye with early/intermediate disease who take particular combinations of high-dose antioxidant vitamin plus zinc supplements daily are at a reduced risk of developing neovascular AMD. This intervention did not prevent the progression to late atrophic AMD significantly, although there was a trend to benefit.[7] A further study, AREDS2, evaluated the efficacy and safety of lutein plus zeaxanthin and/or omega-3 long-chain polyunsaturated acid (LCPUFA) supplementation in reducing the risk of developing advanced AMD.[8] AREDS2 results suggest that lutein/zeaxanthin could be more appropriate than beta carotene in the AREDS1 supplements, and would avoid concerns about potential increased cancer risk associated with beta carotene in ex or current smokers. [9] Although there are other studies evaluating alternative combinations of nutritional supplements to AREDS to protect from progression to late AMD, trials other than AREDS reveal little evidence for effectiveness of antioxidant vitamin and mineral supplements for preventing visual loss or progression of the disease.[10] The Cochrane systematic review stated that as AREDS is a large, well-conducted randomised study, potential biases will have been minimised, hence this study concentrated on AREDS.[10]

A number of studies have evaluated the potential public health impact of AREDS supplements. Bressler and co-workers 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.[11] Other studies assessed the cost effectiveness of vitamin supplements but had limitations relating to the standard of care comparison (e.g. included screening or excluded anti-VEGF therapy) or had limitations in the underlying model (e.g. used a monocular model).[12] Hopley et al, did estimate the cost-effectiveness of vitamins (approximately $31 800 [£18 948] in 2003—per quality adjusted life year [QALY]) but included the cost of diagnostic screening as part of the vitamin intervention and did not

include the cost burden of treating neovascular AMD.[13] A more recent study from Japan addressed the issues of visual loss at a binocular level and the cost of treating neovascular AMD, but included the cost of screening in the analysis. In addition, the study initiated AREDS intervention when 'prodromal' symptoms occurred and used Japanese costings.[14] However, they each have limitations if translated to the current state of AMD management, with the widespread use of anti-VEGF agents to treat neovascular AMD. Anti-VEGF therapy was not routinely available by 2007 when three of the four studies were completed. In addition, economic modelling has evolved since 2007, and none of the papers to date adequately looked at the disorder at a patient level as opposed to individual eye level. Patient level analysis has implications in terms of impact on patient function if CNV develops in the better seeing eye using similar models to those used in NICE health economic reviews. [4]

In the UK currently, there is no formal screening for intermediate or late AMD as defined by Beckman classification,[15] approximately equivalent to AREDS category 3 & 4 patients.

At present, AREDS-type formulations are not routinely funded or prescribed throughout the UK, with some exceptions based on local prescribing rules. Although AREDS had a positive outcome, organisations like NICE have not evaluated these supplements for cost effectiveness possibly as they are not licensed as a drug, although NICE may consider evaluations of public health interventions. In contrast the Veterans Administration in the USA have provided AREDS supplements to patients for public health reasons

This study uses an economic model to investigate the cost-effectiveness of prescribing antioxidants plus zinc (either AREDS 1 or 2 formulations or AREDS 2 for current or ex-smokers) for cases of AMD diagnosed in the course of routine ophthalmic eye care compared with no use of AREDS supplements. We did not model the effect of either antioxidants alone or zinc alone. For clarity, we will define AREDS supplements in this manuscript to contain 500 milligrams of vitamin C; 400 International Units of vitamin E; 15 mg of beta-carotene; 80 mg of zinc; and two mg of copper and AREDS2 supplements to contain 500 milligrams of vitamin C; 400 International Units of vitamin E; 10 mg lutein and 2mg zeaxanthin; 80 mg of zinc; and two mg of copper. Both formulations are commercially available from a variety of manufacturers. We determined the impact of taking AREDS supplements for all patients older than 55 years with AMD using United Kingdom cost and prevalence data.

Methods

Patient population

Patients with either AREDS category 3, bilateral intermediate age-related macular degeneration, or AREDS category 4 subgroup with unilateral neovascular AMD (nAMD), that have previously been shown to benefit from AREDS 1 or 2 supplements were the population of patients modelled.

Model structure

A Markov approach was used to develop a patient level, binocular simulation model using one month cycles. At the beginning of the simulation two paired virtual patients were simulated with the same age, gender, disease state of both eyes, and visual acuity of both eyes(Supplementary Figure 1) One patient was assigned to be treated with AREDS supplements and the other virtual patient was assigned to no treatment. At each simulation cycle, probability of death was applied using linearly interpolated life tables for the corresponding age and gender. Disease progression, treatment costs, and utility was calculated at each cycle. Utility was calculated using the best vision of the two eyes using Brown et al. for the base case.[16] The time horizon for each patient was until the patient died.

Category 3 simulation

At the beginning of the simulation the age and gender of the paired virtual patients were drawn from scaled beta distributions fitted to the data collected from the AREDS trial for category 3. (Supplementary Figure 2) Both eyes were set to intermediate AMD and the vision of both eyes were also drawn from scaled beta distributions from the starting vision of category 3 patients in the AREDS trial. Using the Kaplan Meier curve of category 3 patients time to development of neovascularization in the first eye in the AREDS trial, the time to development of CNV was sampled for one random eye depending on which treatment group the virtual patient was in. Time to development of the second eye was sampled from the Kaplan-Meier curve using the Category 4a with prior neovascularization. A conservative approach was used in that if the time horizon extended past the end of the AREDS trial data (5 years) then the patient was assumed to not have progressed to neovascular AMD in the corresponding eye.

Category 4a with prior neovascularization simulation

At the beginning of the simulation the age and gender of the paired virtual patients were drawn from scaled beta distributions fit to the data collected from the AREDS trial for category 4a with prior neovascularization. (Supplementary Figure 3) One eye was set to intermediate AMD, and the other eye was set to neovascular AMD. The vision of both eyes were also drawn from scaled beta distributions from the starting vision of category 4a with prior neovascularization in the AREDS trial depending on the disease state. Using the Kaplan Meier curve of category 4a with prior neovascularization time to development of neovascularization in the second eye in the AREDS trial, the time to development of CNV was sampled for the intermediate AMD eye. A conservative approach was used in that if the time horizon extended past the end of the AREDS trial data (5 years) then the patient was assumed to not have progressed to neovascular AMD.

In both models, once progression to CNV occurred, the starting vision was adjusted by drawing from a scaled beta distribution of change in ETDRS letters from baseline as noted in the AREDS trial when CNV occurred. If the patient's vision after progression to CNV was better than 6/12 (20/40), the patient eye was deferred treatment based on the EMR data.[14] Once the vision fell below 6/12, the patient eye was entered into the Markov model for transitioning visual acuities.

The Markov model after initiating treatment for neovascular AMD consisted of five health states: five health states defined by declining VA ranging from 6/12 or better (least severe) to less than 3/60 (most severe). This model structure was consistent with the model developed by the Evidence Review Group (ERG) in the original NICE appraisal of ranibizumab for nAMD.[3]
A patient was then treated with three initial monthly ranibizumab injections followed by PRN. Using the EMR data, the probability of requiring an injection in the first year of treatment following the first three injections was calculated. For years beyond the first year, the probability of requiring an anti-VEGF injection each month was assumed to be the same as measured in the second year. These monthly probabilities were drawn from a scaled beta distribution after fitting to the EMR data. Patients were charged for monthly visits after beginning treatment in the first eye. After both eyes progressed to wet AMD, the AREDS supplement were stopped. Each model and sensitivity analysis was run for a total of 100,000 virtual patients in each arm.

Perspective
The perspective of the model was the UK NHS and Personal Social Services (PSS) as recommended in the NICE Guide to the Methods of Technology Appraisal reference case.[17]The model was run until the absorbing state of death was reached, which represented the time horizon used in pivotal trials. Owing to the long horizon, costs and benefits were modelled with discounting of 1.5% per year as recommended for public health interventions.

Utility
Benefits were measured in quality-adjusted life years (QALYs). VA was converted to utility for the calculation of QALYs using Brown et al,[13] which elicited utilities in 80 patients with AMD using the time trade-off method and grouped these by the VA health states defined in the model. The health state utility values used in the model are reported in table 1 and are consistent with those applied to the model used by the ERG in the original NICE appraisal of ranibizumab for nAMD.[18]Utilities were accumulated for the best vision of the two eyes

Table 1: Utility values for model health states

Visual acuity	Utility, mean (SD)
From 6/6 to >6/12	0.89 (0.16)
6/12 to 6/24	0.81 (0.20)
6/24 to 6/60	0.57 (0.17)

6/60 to 3/60	0.52 (0.24)
<3/60	0.40 (0.12)

Source: Brown *et al.*[16]

Costs

Resource use and costs were applied to reflect UK clinical practice. Resource use consisted of regular assessment visits once nAMD was diagnosed and ranibizumab injection given on a PRN basis. At the start of treatment, patients received three initiating doses of ranibizumab as recommended by clinical guidance followed PRN injections at a frequency calculated from the data set. UK unit costs were assigned for a cost year of 2012. A cost of ranibizumab of £551.00 per injection, an assessment cost of £255.00 and a monitoring cost of £60.00 was used. [19] [20] These costs were consistent with the NICE costing template for aflibercept. [21]

Sensitivity analysis

Appropriate probability functions were fitted to model parameters to incorporate uncertainty. Probabilistic sensitivity analysis was performed using a Monte Carlo simulation to randomly sample each parameter. Utilities were characterised by a β distribution, with α and β parameters defined by the means and SDs of the utilities. Costs were characterised by a γ distribution with α and β parameters defined by the means and SDs of the costs. SDs were not available for costs, therefore they were assumed to be 10% of the mean in line with recommended practice for health economic models. Transition probabilities were characterised by a beta distribution. For each PSA parameter, 200,000 virtual patients were simulated until death. A total of 1,000 PSA simulations were run for each model. One-way sensitivity analysis was employed to test structural uncertainty within the model.

AREDS data set

Investigators of this study had full access to the cleaned but unanalysed AREDS dataset to develop this model. Details of AREDS design have been previously published and are briefly described. [22] Between November 13, 1992, and January 15, 1998, 4757 persons aged 55 to 80 years at the time of enrolment were entered into the study at 11 clinical centres. The ocular eligibility requirements were largely determined by the AMD component findings of AREDS. Macular status was assessed, using the AREDS system for classifying age-related macular degeneration, [22] by trained and certified readers at a reading centre, based on stereoscopic colour fundus photographs taken at baseline and at regular intervals during follow-up. Except for the requirement that all participants have at least 1 eye with a visual acuity of 20/32 or better and that the media be sufficiently clear for reasonable quality fundus photography, no other exclusion criteria were applied. Visual acuity was measured in each eye by the Early Treatment of Diabetic Retinopathy Study (ETDRS) method as the number of letters read correctly. AREDS2 data was not used as there was no placebo group in the study.[23]

EMR data set

We have previously described the methodology of obtaining the large data set of 92 976 ranibizumab injections,[17][18] as well as the effectiveness and cost effectiveness of treating with ranibizumab at visual acuities better than 6/12[24 25], which covered data from the approval of ranibizumab in August 2008 until April 2012. In brief, 14 NHS hospitals that deliver ranibizumab AMD treatment services in England and Northern Ireland submitted data to this study. Each site is the only NHS provider of nAMD care to their local population and very few patients switch between providers. Following NICE approval for the use of ranibizumab for nAMD in the NHS in August 2008, all sites used this drug almost exclusively. The lead clinician and Caldicott Guardian (who oversees data protection) at each centre gave written approval for the data extraction. Patient identifiers were completely stripped out, and site and clinician data were pseudo-anonymised, and on this basis an ethics committee determined that formal ethics approval was not required. This study was conducted in accordance with the declaration of Helsinki and the UK's Data Protection Act. The 14 sites entered their first treatment episodes into the EMR system during the following years: 2006 (n=2 sites), 2007 (n=5), 2008 (n=4), 2009 (n=1) and 2010 (n=2). The first recorded ranibizumab injection was dated November 2006. Over the period of data collection, anti-VEGF treatment was performed in 13 774 patients, of whom 2639 received anti-VEGF for reasons other than nAMD or received bevacizumab. Thus, this study analyses data on 12 951 eyes of 11 135 patients who received a total of 92 976 ranibizumab injections during 317 371 clinic visits at 14 UK hospitals. In total, 16.3% (n=1816) of these patients required treatment to both eyes during the follow-up period. The demographics of the patients included have previously been described and are summarised in supplementary material table 1. 'Best-measured VA' was the best VA with refraction or habitual correction and/or pinhole as measured on ETDRS chart and expressed as ETDRS letters and LogMAR vision in this study.

Missing EMR data

For patients whose data were not available for a particular visit or had been lost to follow-up, no missing value substitutions were performed. The only exception to this rule was baseline VA, as some treatment centres brought patients back for a two stop service—assessment on first visit followed by injection on second visit, and did not repeat VA measurements on the date of the first injection (n=1670), which was always performed within 3 weeks. This was therefore not missing data per se but reflects variation in treatment delivery. In the model, we assumed no differences between centres for resource use associated with service delivery.

Results

The simulation results showing transitioning of patients into different AMD states or death is summarised in Figure 1a for AREDS 3 patients and Figure 1b for AREDS category 4 patients over 125 months.

For AREDS category 3, our model showed that the treatment group accumulated 13,785 GBP (17,780 USD) per patient lifetime whereas the untreated group accumulated 12,879 GBP (16,611 USD) per patient lifetime. Accumulated health benefits were 11.53 QALYs per patient in the treatment group compared to 11.52 QALYs per patient in the treatment group. This translates to a beneficial intervention driven by a mean of 3.07 fewer anti-VEGF injections in the treated group but at increased cost with an ICER of 30197. PSA analysis showed similar trends and the one way sensitivities are shown in Table 2 & Figure 2.

Table 2 Category 3 Results
Each one way / base is 50 x 200,000 simulated pts (100,000 treated, 100,000 controls)

	No vitamins			**Vitamins**			**ICER**
	Cost (GBP)	Benefit (QALYs)	Injections (n)	Cost (GBP)	Benefits (QALYs)	Injections (n)	
							30,197.00
Base	**12,879.06**	**11.52**	**17.69**	**13,784.97**	**11.55**	**14.62**	
Avg PSA results (SD)	12,863.39 (1,061.45)	11.50 (0.37)	17.70	13,762.03 (922.27)	11.55 (0.37)	14.63	17,972.80
Discount = 3.5%	9,916.39	9.61	17.72	10854.39	9.64	14.63	31,266.67
Espallargues SF-6D	12,904.45	9.27	17.70	13,769.34	9.28	14.59	86,489.00
Free Vitamin cost	12,877.14	11.51	17.68	10,910.96	11.56	14.63	-39,323.60
Immediate treatment	12,919.43	11.67	17.75	13,818.56	11.68	14.67	89,913.00
Bevacizumab	5,686.77	11.52	17.70	7,809.02	11.56	14.61	53,056.25

For AREDS category 4a with prior neovascularization, our model showed that the treatment group accumulated 52,074 GBP (67,165 USD) per patient lifetime whereas the untreated group accumulated 54,900 GBP (70,810 USD) per patient lifetime. Accumulated health benefits were 10.59 QALYs in the treatment group compared to 10.43 QALYs in the treatment group. This translates to a cost-negative yet beneficial intervention driven by a mean of 7.67 fewer anti-VEGF injections in the treated group. PSA analysis showed similar trends and the one way sensitivities are shown in Table 3 and Figure 3.

Table 3 Category 4 Results
Each one way / base is 50 x 200,000 simulated pts (100,000 treated, 100,000 controls)

*Note ICER values are negative(*) and in the south east corner of the cost effectiveness plane [26]

	No vitamins			Vitamins			
	Cost (GBP)	Benefits (QALYs)	Injections (n)	Cost (GBP)	Benefits (QALYs)	Injections (n)	ICER
Base	**54,899.63**	**10.43**	**71.02**	**52,074.31**	**10.59**	**63.38**	**-17,658.25***
Avg PSA results (SD)	54,849.73 (4,716.82)	10.42 (0.40)	71.02	52,021.32 (4,228.21)	10.58 (0.37)	63.38	-17,677.56*
Discount = 3.5%	45,862.29	8.78	71.07	43,609.89	8.91	63.37	-17,326.15*
Espallargues SF-6D	54,891.09	8.70	71.03	52,059.64	8.72	63.39	-141,572.50*
Free Vitamin cost	54,894.43	10.43	71.01	50,036.92	10.59	63.38	-30,359.44*
Immediate treatment	54,977.62	11.13	71.13	52,132.07	11.12	63.47	-284,555.00*
Bevacizumab	24,190.49	10.43	71.02	24,621.46	10.59	63.36	2,693.56

Discussion

Intervention with AREDS supplements is likely to be a dominant cost effective strategy in category 4 patients with neovascularization in one eye. Over the lifetime of the patient, patients received an average 7.67 less intravitreal injection (lower cost) and gained 0.16 QALYs compared with no use of supplements. In patients with bilateral intermediate AMD, AREDS category 3, the ICER of £30,197 of in versus current treatment practice is substantially below a threshold of £20 000 per QALY, which is often considered the NHS's willingness to pay.

Numerous nutritional supplements are available commercially, but very few robust studies have been conducted. A Cochrane review identified one large study (AREDS) that has minimal bias that is of benefit in patient with AMD. The same report stated that other smaller trials with shorter follow-up do not provide evidence of any benefit.[10] This health economic evaluation concentrated therefore on the AREDS supplements from the AREDS trial and assumed equivalency of AREDS2 supplements, data from which were not available at the time of the Cochrane review. What has not been demonstrated clearly to date is their cost-effectiveness utilising a health economic model for the UK setting, utilising data from both eyes, and the costings and implications of developing nAMD requiring treatment with anti-VEGF (ranibizumab or aflibercept).

This study demonstrates that intervention with AREDS supplements (1 or 2), would be a dominant health intervention, as it both lowers costs and leads to better visual outcomes. This is an intervention that would be on the "south- east corner" of the cost effectiveness plane, and so an estimated ICER is not reported. [26]

The main driver of cost effectiveness is the cost of anti-VEGF therapy therefore if costs of therapy were to come down significantly, through the widespread use of avastin for example, the results may change. However, we tested different prices in one-way sensitivity analysis and found results for category 4 AREDS to remain a dominant intervention.

Risks of supplements

Several factors may be considered regarding the potential risks or side effects. First, in the original AREDS report, hospitalizations for genitourinary diseases were significantly more common in participants randomized to receive AREDS supplements than to receive placebo (11% versus 8%). These hospitalizations were mainly due to urinary tract infections in men and were not related to malignancies nor were associated with increased mortality in the zinc group. However in AREDS2, rates of reported gastrointestinal disorders and hospitalizations for genitourinary diseases were similar in the 2 randomly assigned groups (high-dose zinc, low-dose zinc). Second, AREDS supplements reduce the burden of nAMD that require anti-VEGF agents which is associated with a risk of endophthalmitis and possible excess stroke risk. In a pooled analysis of 2-year controlled studies, the stroke rate was 2.7% in patients treated with 0.5 mg ranibizumab compared to 1.1% in patients in the control arms (odds ratio 2.2 [95% confidence interval (0.8-7.1). Third, the long-term safety profile of lutein/zeaxanthin supplementation is not well-known. The substitution of these compounds for beta carotene, seems reasonable, given their potential benefit as well as safety concerns related to increased risk of lung cancer in smokers using beta carotene containing supplements, [27] and the findings of AREDS2 that there were more lung cancers noted in the beta carotene vs no beta carotene group (23 [2.0%] vs 11 [0.9%], nominal P = .04), mostly in former smokers. Our model assumed that current or ex-smokers used AREDS2 supplements and no alteration in lung cancer burden or mortality was assumed. However, possible long-term effects and possible adverse events associated with lutein/zeaxanthin supplementation are not yet known although there seems to be no medium term adverse events.

AREDS2

While primary analysis from the AREDS2 did not reveal additional benefit of daily supplementation with lutein/zeaxanthin on AMD progression, secondary exploratory analyses suggested that lutein/zeaxanthin were helpful in reducing this risk.[9 27] We assumed equivalency of AREDS1 supplements and AREDS2 combination of substituting beta carotene.

Limitations

We did not model the risks of possible excess hospital admissions due to genitourinary problems that may be associated with AREDS or the reduced risk of endophthalmitis or possible stroke that AREDS could prevent by reducing anti-VEGF injection need. Given the cost of managing stroke and endophthalmitis is likely to be greater than the cost of managing a slight increase in genitourinary problems, this is unlikely to alter the conclusions of our analysis.

We assumed excellent compliance of AREDS supplements in patients in category 4 AREDS with nAMD in the first eye, as they would likely be highly motivated to prevent visual loss in

the second eye. A survey of European ophthalmologists suggest that 29% of stage 4 AREDS patients were non-compliant taking them, which is similar to the 20% non-compliance rate in the original AREDS.[9 28] However, it may be that compliance is poor in category 3 AREDS patients. A possible public health strategy may be only to actively supply AREDS to category 4 neovascular AMD patients, given that 11% of patient with AREDS did not take AREDS supplements in a survey citing cost as a main factor.[28]

We believe that an evaluation of the clinical and economic impacts of AREDS supplements as a public health intervention would be warranted by NICE. While we have not estimated the full budget impact of introducing AREDS supplements in the UK, we estimate that the cost of such an intervention in the first year in category 4 patients would be £6.99mn per year, assuming all patients take AREDS supplements with similar compliance as AREDS (based on Owen et al. estimate of 31,006 new cases of neovascular AMD per year and the proportion that would be unilateral)[29, 30]. This would be offset over the lifetime of the patient through fewer intravitreal injections. Undiscounted, this could save £131mn of ranibizumab injections over a lifetime for this first year cohort based on the costs and treatment strategies used in this model.

In conclusion in this model demonstrates that the use AREDS supplements is a dominant cost effective intervention for use for AREDS category 4a patients with neovascular AMD in one eye in the UK.

Previous studies have supported the effectiveness of AREDS supplements for Category 3 and 4 patients. From this study the recommendation to publicly fund AREDS supplements to category 3 patients would depend on the health care system willingness to pay. In contrast AREDS supplements are a dominant cost-effective intervention for Category 4 AREDS patients, as they are both less expensive than standard care and more effective and therefore should be considered for public funding

Figure Legends

Figure 1: (A) Simulation results for AREDS Category 3 patients over 125 months. (B) Simulation results for AREDS Category 4 patients over 125 months

Figure 2: Costs and QALYs accumulated by Category 3 patients treated with AREDS supplements according to current NHS practice (red) and with intervention (blue). GBP, British Pounds; NHS, National Health Service; QALY, quality-adjusted life year.

Figure 3: Costs and QALYs accumulated by Category 4 patients treated with AREDS supplements according to current NHS practice (red) and with intervention (blue). GBP, British Pounds; NHS, National Health Service; QALY, quality-adjusted life year.

Supplementary Table 1

Immediate treatment

First three months (months 0-2), probability for 3 month cycle	To 6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
From 6/6 to >6/12	.7240143	.2222222	.0334528	.0107527	.0095579
Rest of two years (months 3-24), probability for 1 month cycle	To 6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
From 6/6 to >6/12	.8777667	.1162512	.0045862	.0005982	.0007976
6/12 to 6/24	.2937467	.6242775	.0782974	.0031529	.0005255
6/24 to 6/60	.0359281	.2355289	.6746507	.0479042	.0059880
6/60 to 3/60	.0218978	.0145985	.1532847	.7007299	.1094891
<3/60	.0588235	.0147059	.0147059	.2058824	.7058824

Delayed treatment

First three months (months after drop to state 2), probability for 3 month cycle	To 6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
From 6/6 to >6/12	.0	.0	.0	.0	.0
6/12 to 6/24	.3299857	.4992826	.1506456	.0138690	.0062171
6/24 to 6/60	.0699413	.3048585	.4922584	.1057128	.0272290
6/60 to 3/60	.0156919	.0927247	.3794579	.4122682	.0998573
<3/60	.0202703	.0540541	.2432432	.4256757	.2567568
Rest of two years (+ 3 from months after reaching state 2), probability for 1 month cycle	To 6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
From 6/6 to >6/12	.7365606	.2408118	.0138508	.0026056	.0061711
6/12 to 6/24	.1433278	.7160901	.1340708	.0054130	.0010983
6/24 to 6/60	.0081088	.1414247	.7368559	.1068097	.0068009

6/60 to 3/60	.0047253	.0092538	.2018114	.7044694	.0797401
<3/60	.0380048	.0087094	.0459224	.2984956	.6088678

References

1. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology 2012;**119**(3):571-80 doi: 10.1016/j.ophtha.2011.09.027.
2. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K, Group S-US. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology 2013;**120**(11):2292-9 doi: 10.1016/j.ophtha.2013.03.046.
3. National Institute for Health and Care Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration, 2008. https://www.nice.org.uk/guidance/ta155 (accessed 20 Mar 2017)
4. National Institute for Health and Care Excellence. Aflibercept solution for injection for treating wet age-related macular degeneration. Final appraisal determination 2013. . https://www.nice.org.uk/guidance/ta294 (accessed 20 Mar 2017)
5. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014;**121**(1):193-201 doi: 10.1016/j.ophtha.2013.08.01.
6. Gillies MC, Nguyen V, Daien V, Arnold JJ, Morlet N, Barthelmes D. Twelve-Month Outcomes of Ranibizumab vs. Aflibercept for Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 2016;**123**(12):2545-53 doi: 10.1016/j.ophtha.2016.08.016.
7. 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. Archives of ophthalmology 2001;**119**(10):1417-36
8. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;**309**(19):2005-15 doi: 10.1001/jama.2013.4997.
9. Aronow ME, Chew EY. Age-related Eye Disease Study 2: perspectives, recommendations, and unanswered questions. Current opinion in ophthalmology 2014;**25**(3):186-90 doi: 10.1097/icu.0000000000000046.
10. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. The Cochrane database of systematic reviews 2012;**11**:CD000254 doi: 10.1002/14651858.CD000254.pub3.
11. Bressler NM, Bressler SB, Congdon NG, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. Archives of ophthalmology 2003;**121**(11):1621-4 doi: 10.1001/archopht.121.11.1621.
12. Rein DB, Saaddine JB, Wittenborn JS, et al. Cost-effectiveness of vitamin therapy for age-related macular degeneration. Ophthalmology 2007;**114**(7):1319-26 doi: 10.1016/j.ophtha.2006.10.041.
13. 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**(4):450-4
14. Tamura H, Goto R, Akune Y, Hiratsuka Y, Hiragi S, Yamada M. The Clinical Effectiveness and Cost-Effectiveness of Screening for Age-Related Macular Degeneration in Japan: A Markov Modeling Study. PloS one 2015;**10**(7):e0133628 doi: 10.1371/journal.pone.0133628.
15. Ferris FL, 3rd, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. Ophthalmology 2013;**120**(4):844-51 doi: 10.1016/j.ophtha.2012.10.036.

16. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. Archives of ophthalmology 2000;**118**(1):47-51
17. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword (accessed 20 Mar 2017)
18. National Institute for Health and Care Excellence. Ranibizumab for the treatment of diabetic macular oedema. https://www.nice.org.uk/guidance/ta274 (accessed 20 Mar 2017)
19. Health and Social Care Information Centre. Hospital Episode Statistics 2011/12.. http://www.hscic.gov.uk/hes.
20. Electronic Medicines Compendium. Secondary Electronic Medicines Compendium. http://www.medicines.org.uk/emc/.
21. National Institute for Health and Care Excellence. Aflibercept solution for injection for treating wet age‐related macular degeneration- costing template. https://www.nice.org.uk/guidance/ta294/resources. (accessed 20 Mar 2017)
22. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. Controlled clinical trials 1999;**20**(6):573-600
23. Group AR, Chew EY, Clemons T, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). Ophthalmology 2012;**119**(11):2282-9 doi: 10.1016/j.ophtha.2012.05.027.
24. Lee AY, Lee CS, Butt T, et al. UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. Br J Ophthalmol 2015 doi: 10.1136/bjophthalmol-2014-306229.
25. Butt T, Lee A, Lee C, Tufail A; UK AMD EMR Study Group. The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes. BMJ Open. 2015 May 5;5(5):e006535.doi: 10.1136/bmjopen-2014-006535.
26. Klok RM, Postma MJ. Four quadrants of the cost-effectiveness plane: some considerations on the south-west quadrant. Expert Rev Pharmacoecon Outcomes Res. 2004 Dec;4(6):599-601. doi: 10.1586/14737167.4.6.599.
27. Chew EY, Clemons TE, Sangiovanni JP, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA ophthalmology 2014;**132**(2):142-9 doi: 10.1001/jamaophthalmol.2013.7376.
28. Aslam T, Delcourt C, Holz F, et al. European survey on the opinion and use of micronutrition in age-related macular degeneration: 10 years on from the Age-Related Eye Disease Study. Clin Ophthalmol 2014;**8**:2045-53 doi: 10.2147/opth.s63937.
29. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. Br J Ophthalmol. 2012 May;96(5):752-6. doi: 10.1136/bjophthalmol-2011-301109
30. Wilde C, Poostchi A, Mehta RL, et al. Prevalence of age-related macular degeneration in an elderly UK Caucasian population-The Bridlington Eye Assessment Project: a cross-sectional study. Eye 2017 Jul;31(7):1042-1050. doi: 10.1038/eye.2017.30.