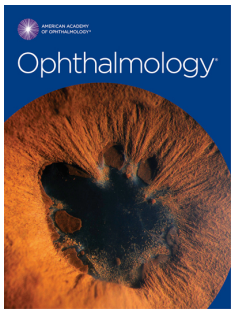

Age-Related Macular Degeneration Preferred Practice Pattern®

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AMERICAN ACADEMY OF OPHTHALMOLOGY®

Age-Related Macular Degeneration Preferred Practice Pattern®

Elsevier to replace this cover page with the color PDF.
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RETINA/VITREOUS PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Retina/Vitreous Preferred Practice Pattern® Panel** members wrote the Age-Related Macular Degeneration Preferred Practice Pattern® (PPP) guidelines. The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

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We thank our partners, the Cochrane Eyes and Vision US Satellite (CEV@US), for identifying reliable systematic reviews that we cite and discuss in support of the PPP recommendations.

The Preferred Practice Patterns Committee members reviewed and discussed the document during a meeting in June 2019. The document was edited in response to the discussion and comments.

Preferred Practice Patterns Committee 2019
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The Age-Related Macular Degeneration PPP was then sent for review to additional internal and external groups and individuals in July 2019. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the Retina/Vitreous Preferred Practice Pattern Panel reviewed and discussed these comments and determined revisions to the document.

FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx). A majority (88%) of the members of the Retina/Vitreous Preferred Practice Pattern Panel 2018–2019 had no financial relationship to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2019 are available online at www.aao.org/ppp.

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OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved U.S. Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the approved by date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at www.aao.org/about-preferred-practice-patterns) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Age-Related Macular Degeneration PPP are ophthalmologists.

METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined by the PPP Panel to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. Ratings are embedded throughout the PPP main text in italics.
- Literature searches to update the PPP were undertaken in March 2018 and June 2019 in PubMed and the Cochrane Library. Complete details of the literature searches are available online at www.aao.org/ppp.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

Although an estimated 80% of age-related macular degeneration (AMD) patients have non-neovascular or atrophic AMD, the neovascular form is responsible for the majority of the severe central visual acuity (VA) loss associated with AMD.

The primary risk factors for the development of advanced AMD include increasing age, northern European ancestry, and genetic factors. Cigarette smoking is the main modifiable risk factor that has been consistently identified in numerous studies. Smoking cessation is strongly recommended when advising patients who have AMD or are at risk for AMD. The routine use of genetic testing is not recommended at this time.

A meta-analysis of 10 studies found that the use of aspirin was not associated with an increased risk of AMD. Therefore, patients who have been instructed by a physician to use aspirin should continue to use it as prescribed.

Antioxidant vitamin and mineral supplementation as per the Age-Related Eye Disease Study (AREDS2) should be considered in patients with intermediate or advanced AMD. There is no evidence to support the use of these supplements for patients who have less than intermediate AMD and no evidence of any prophylactic value for family members without signs of AMD.

Fluorescein angiography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) are useful diagnostic tests in clinical practice to detect new or recurrent neovascular disease activity and guide therapy.

In patients with neovascular AMD, early detection and prompt treatment improves the visual outcome. Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.

INTRODUCTION

DISEASE DEFINITION

Age-related macular degeneration (AMD) is a disorder of the macula characterized by one or more of the following (for specific terms, see Glossary):

- Presence of at least intermediate-size drusen (≥63 μm in diameter)
- Retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- Presence of any of the following features: geographic atrophy of the RPE, choroidal neovascularization ([CNV] exudative, wet), polypoidal choroidal vasculopathy (PCV), reticular pseudodrusen, or retinal angiomatous proliferation

This Preferred Practice Pattern uses the classification of the Age-Related Eye Disease Study (AREDS) and a more recent clinical classification[4] to define the early and intermediate stages of AMD because current treatment recommendations are based on these classifications. The AREDS was a prospective multicenter randomized clinical trial conducted between 1992 and 2006 designed to assess the natural course and risk factors for age-related cataract and AMD. The effects of antioxidant vitamins and minerals on these two ocular conditions were studied.

The classification of AMD from the AREDS is as follows:[5]

- *No AMD* (AREDS category 1) represented the control group; it is characterized by no or few small drusen (<63 μm in diameter).
- *Early AMD* (AREDS category 2) is characterized by a combination of multiple small drusen, few intermediate drusen (63–124 μm in diameter), or mild RPE abnormalities.
- *Intermediate AMD* (AREDS category 3) is characterized by any of the following features:
  - Numerous intermediate drusen
  - At least one large druse (≥125 μm in diameter)
  - Geographic atrophy (a sharply demarcated, usually round or oval, area of atrophy of the RPE not involving the center of the fovea)
- *Advanced AMD* (AREDS category 4) is characterized by one or more of the following (in the absence of other causes) in one eye:
  - Geographic atrophy of the RPE involving the foveal center
  - Neovascular maculopathy that includes the following:
    - CNV defined as pathologic angiogenesis originating from the choroidal vasculature that extends through a defect in Bruch's membrane
    - Serous and/or hemorrhagic detachment of the neurosensory retina or RPE
    - Retinal hard exudates (a secondary phenomenon resulting from chronic vascular leakage)
    - Subretinal and sub-RPE fibrovascular proliferation

- Disciform scar (subretinal fibrosis)

See Glossary for definitions of important terms. Clinical details are available in standard texts.[6,7]

PATIENT POPULATION

Patients are typically aged 50 years or older, with or without visual symptoms. Clinicians should consider the possibility of hereditary macular dystrophies in patients under 50 years of age who have clinical features that resemble AMD.

CLINICAL OBJECTIVES

- Identify patients at risk of visual loss related to AMD
- Educate patients and their families about the disease, risk factors, and preventive measures
- Minimize or reverse visual loss and functional impairment in these patients through appropriate detection, self-assessment, treatment, and follow-up examinations
- Help patients identify expert physicians and resources needed to facilitate improvement in vision

BACKGROUND

INCIDENCE AND PREVALENCE

Age-related macular degeneration is a leading cause of severe, irreversible vision impairment in developed countries.[8-13] In 2004, it was estimated that approximately 1.75 million people aged 40 years or older in the United States have advanced AMD, either neovascular AMD or geographic atrophy in at least one eye; and 7.3 million were considered to have high-risk features, such as large drusen (≥125 µm in diameter) in one or both eyes.[12] The authors projected that the number of individuals affected by advanced AMD in at least one eye will increase to nearly 3 million by year 2020,[12] based on the aging population demographics in the United States.[14] Aging is the greatest risk factor; therefore, the prevalence of AMD in the United States is anticipated to increase to 22 million by the year 2050, while the global prevalence is expected to increase to 288 million by the year 2040.[15] These predictions are likely to be affected by both more effective treatments for the neovascular forms of AMD using anti-vascular endothelial growth factor (VEGF) agents as well as the slowing of the disease progression using antioxidant vitamins with zinc. The use of anti-VEGF agents will likely reduce the odds of legal blindness from neovascular AMD and could theoretically reduce the rate of legal blindness by up to 70% over 2 years.[16] However, longer-term follow-up studies from the population originally treated with regular anti-VEGF agents suggest that these gains in visual acuity (VA) are largely lost in two-thirds of patients followed for over 7 years.[17] The use of antioxidant vitamins (i.e., vitamin C, vitamin E), lutein, zeaxanthin, and zinc in an otherwise well-nourished population with intermediate AMD has been demonstrated to reduce the progression toward more advanced stages of AMD by approximately 25% at 5 years.[5,18] A study forecasting the

potential impact of treatments in AMD concluded that though the prevalence of AMD will increase substantially by 2050 in the United States, the use of anti-VEGF therapies and vitamin therapies will mitigate these effects.[19]

Overall, AMD is responsible for an estimated 46% of cases of severe visual loss (VA 20/200 or worse) in persons over age 40 in the United States.[13] While most consider the onset of AMD as occurring in individuals over the age of 50, there are variations in the epidemiologic literature. While relatively few cases of advanced AMD occur between ages 40 and 50, detection of earlier AMD stages, which are precursors of more advanced AMD, are not uncommon occurrences during this decade. Therefore, the reader must keep in mind that AMD is a disease spectrum that has early and later stages. Although an estimated 80% of AMD patients have non-neovascular or atrophic AMD,[9] the neovascular form with its natural history is responsible for nearly 90% of the severe VA loss (20/200 or worse) from AMD.[20,21]

The prevalence, incidence, and progression of AMD and most associated features (e.g., large drusen) increase with age. The prevalence of AMD also varies by ethnicity.[13,22-24] In the Beaver Dam Eye Study, consisting of primarily a Caucasian population base, the prevalence of any AMD (referred to as age-related maculopathy) was less than 10% in persons aged 43 to 54 years yet more than tripled for persons aged 75 to 85 years of age.[8] The Beaver Dam Eye Study demonstrated that the development of any AMD over a 10-year period was 4.2% for persons 43 to 54 years old and 46% for those 75 and older.[25] The Beaver Dam Eye Study has identified that soft, indistinct drusen and pigmentary abnormalities also increase in frequency with increasing age and are strongly predictive of progression to more advanced AMD. In the Los Angeles Latino Eye Study, prevalence of advanced AMD increased from 0% in individuals 40 to 49 years old to 8.5% in those 80 years old and older.[26] The Proyecto Vision Evaluation and Research study of Hispanic participants in Arizona found that the prevalence of advanced AMD increased from 0.1% in persons 50 to 59 years old to 4.3% in those 80 and older.[27]

Observations from the Barbados Eye Study,[28] the Baltimore Eye Study,[29] and the Macular Photocoagulation Study (MPS)[30] suggest that late stages of AMD are more common among Caucasians. Findings from the Multi-ethnic Study of Atherosclerosis also suggest that neovascular AMD may be more common in Caucasians than in African Americans.[23] In Asian populations, there are racial variations in the prevalence of early and late AMD, and Caucasian and Asian populations are at higher risk than Hispanic and African individuals.[31-36] A recent meta-analysis and systematic review reported a higher prevalence of AMD in Europeans than in Asians or Africans, with no difference in prevalence between Asians and Africans. The global number of people with AMD was projected to be 196 million in 2020, increasing to 288 million in 2040.[15]

RISK FACTORS

The main risk factors for the development of advanced AMD are increasing age, ethnicity (i.e., Caucasian and family history). Although a number of modifiable risk factors have been investigated, cigarette smoking is the main modifiable risk factor that has been consistently identified in numerous studies.[37-46] Importantly, it is essential to recognize that the associations found in observational studies that analyze risk factors should not be interpreted as cause and effect. Such associations may not necessarily translate into treatment recommendations, as there may be multiple confounding variables that are not accounted for in the studies.

Smoking, Hypertension, and Cardiovascular Disease

Smoking significantly increases the risk of AMD and there appears to be a dose response relationship, because the odds ratio increases with an increased number of pack-year exposure.[39,47] Smoking cessation is associated with a reduced risk of AMD progression; the risk of developing AMD in individuals who have not smoked for more than 20 years is comparable to the risk in nonsmokers.[39] Thus, smoking cessation is strongly recommended when advising patients, as it represents a key and important modifiable risk factor. A number of case-control and population-based studies have examined the relationship between AMD, hypertension, and other cardiovascular diseases. These studies have shown conflicting results.[22,48-54] Passive smoking exposure was associated with an increased risk of AMD (odds ratio 1.87%; 95% confidence interval [CI] 1.03 – 3.40) in non-smokers.[39]

Levels of Antioxidants

Additional risk factors may include low systemic levels of antioxidants. Data from observational studies have been inconsistent in identifying low levels of plasma and dietary antioxidants of vitamins C and E, carotenoids (e.g., lutein, zeaxanthin), and zinc as risk factors for AMD.[55-61] The original AREDS results demonstrated a beneficial effect for the use of high-dose oral antioxidant vitamins (vitamins C, E, beta-carotene) and zinc supplementation in reducing progression of intermediate AMD or advanced AMD in the fellow eye to advanced AMD by 25%.[62] However, additional vitamin E supplementation above the AREDS levels should be avoided.[63] Results of AREDS2 support the removal of beta-carotene (found in the original AREDS supplements) and the addition of lutein/zeaxanthin in the AREDS2 supplements.[18] Furthermore, elimination of the beta-carotene component may reduce the competitive absorption of the lutein/zeaxanthin. Importantly, removal of beta-carotene may also decrease higher incidence of lung cancer associated with the use of supplemental beta-carotene.[64] Finally, AREDS2 demonstrated that there was no effect on the progression of AMD by either reducing the zinc dose (from 80 mg to 25 mg) or adding an omega-3 polyunsaturated fatty acid supplement (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]).[64] A recent Cochrane systematic review concluded that taking antioxidant vitamins plus zinc

probably slows the progression to late AMD and vision loss (moderate-certainty evidence). They also concluded that supplements containing only lutein and zeathanthin may have little or no effect on the progression of AMD.[65]

Diet

Several studies have also identified an association between dietary fat and advanced AMD.[40,66-71] Similar to the reports on risk factors for cardiovascular disease, a number of reports from population-based studies have demonstrated that a reduced risk of AMD is associated with higher dietary intake of foods rich in omega-3 long-chain polyunsaturated fatty acids, such as fish.[40,70-73] In a nested cohort study from the original AREDS population of 1837 patients who were at moderate risk for progression, participants who reported the highest omega-3 intake (note that this was not in the form of a supplement) were 30% less likely to develop advanced AMD after 12 years.[71] These dietary long-chain fatty acids are felt to decrease inflammatory mediators via immunomodulation, thus decreasing disease progression to advanced AMD.[71] An increased risk of AMD was found in individuals who had a higher intake of saturated fats and cholesterol and in those with a higher body mass index.[44] Despite this dietary association, AREDS2 failed to demonstrate a benefit from the use of DHA and EPA as oral supplements at the doses tested; both are omega-3 poly-unsaturated fatty acids.[64] The EYE-RISK consortium recently published their evaluation of the pooled data from the Rotterdam Study-1 and the Alienor Study populations, which included over 4000 participants with mean follow-up of 9.9 years and 4.1 years, respectively, and adherence to Mediterranean diet and found this diet was associated with 41% reduced risk of advanced AMD. The Mediterranean diet includes a diet rich in fruits, vegetables, legumes and fish.[74,75]

Aspirin

Recent observational studies have indicated a possible link between aspirin use and AMD. The Beaver Dam Eye Study reported two times the incidence of late macular degeneration in patients who used aspirin at least twice weekly for 10 years compared with those who used no aspirin.[76,77] Other studies have shown a potential protective effect of aspirin against the development of AMD.[78] In a meta-analysis of 10 studies including over 171,000 patients, the use of aspirin was not associated with an increased risk of AMD.[79] In light of all of the available information on the subject of aspirin use and AMD, the current preferred practice is for patients who have been instructed to use aspirin by a physician to continue their aspirin therapy as prescribed.[80 81]

Genetic Factors

Molecular genetic studies and epidemiologic studies have determined some of the genetic factors in AMD.[82-88] Several studies published in 2005 identified a strong association of the complement factor H (CFH) Y402H polymorphism with a higher risk of AMD.[89-94]

The CFH gene product is involved in regulation of the complement system through binding to factor C3b. This specific complement factor represents a key regulator of the innate rather than the adaptive immune system. An alteration of regulation that occurs as a result of modification at the C3b site leads to a defective regulation of the alternative complement pathway and results in an up-regulation of inflammation to host cells that are mediated by the membrane attack complex. Patients homozygous for the Y402H risk allele of CFH possess a 7.4-fold increased risk of AMD. The CFH gene is located on chromosome 1, in a region linked to AMD in multiple family studies.[89] Studies report an association of a CFH variant (homozygous individuals) with other factors for the risk of progression to advanced AMD compared with noncarriers who lack these determinants.[95,96] Other factors associated with abnormal complement variants and AMD progression include an elevated erythrocyte sedimentation rate, an elevated serum C-reactive protein, and smoking. Such findings support the combined pathogenic mechanisms for AMD progression that include an interplay of environmental factors, heredity, and inflammation.

Strong linkage disequilibrium has been shown across the ARMS2-HTRA1 region, and these two genes are also strongly associated with AMD.[97-99] The exact mechanism that explains this association has not been clearly determined.[100] Other proposed genetic variants associated with AMD include a variant in the hepatic lipase (LIPC) gene[101] and the rs3775291 variant in the toll-like receptor 3 (TLR3) gene.[102,103] A number of other genes have also been identified as well as several other rare variants of genes.[104] A combination of genes and other risk factors may dispose an individual to varying AMD risks more than any one variant taken in isolation.[105] A recent genome-wide association study has identified 19 loci ($P<5x10^{-8}$), seven of which are newly described.[106]

Age-related macular degeneration has a complex genetic background with similar phenotypes. Many genetic associations have been identified—some are protective,[107] some are associated with disease progression, and others have been reported yet not confirmed and require further investigation.

In 2013, several authors proposed that genetic selection of subjects who would most benefit from nutritional supplementation should be used to guide therapy based on a post hoc analysis of a subset of the AREDS population. Thus, the authors recommend using a personalized genetic testing approach to guide therapy in AMD.[108,109] However, an analysis of the AREDS population that included an additional 526 AREDS subjects concluded that genetic testing does not provide benefits in managing nutritional supplements in this population.[110-112]

Statistical experts found errors in the data used to support an association, and bias in the analyses used to support genetic testing. They concluded that there was no evidence to support the need for genotyping to guide recommendations for use of supplements containing antioxidants and zinc in AMD.[113]

A recent prospective, multicenter study looked at genome-wide associations with treatment outcomes in a cohort of 465 patients with exudative AMD who were initiating ranibizumab therapy.[114] Although there was no association of any single-nucleotide polymorphism with 12-month treatment outcomes (i.e., achieving a dry macula, requiring additional treatment, and visual acuity change), the authors found preliminary evidence of a predictive association of the ARMS/HTRA1 polymorphism with the need for additional treatment. They postulated that testing for this polymorphism might be able to predict the frequency of injection after initial ranibizumab therapy. However, a systematic review published in 2015 looked at the association between anti-VEGF response and variations in AMD-associated genes and concluded that genetic background may influence an individual's response to treatment, however further studies are needed to better understand the contribution of various genes to treatment response.[115]

Currently, only post hoc analysis data is available and results are conflicting.[116] One or more prospective clinical trials will need to demonstrate the value of genetic testing in AMD. That is, randomization based on genetic type has not been done for neovascular AMD treatment response to date. Thus, the routine use of genetic testing is not supported by the existing literature and is not recommended at this time.

Other Risk Factors

An increased waist/hip ratio for men has been associated with an increase in the risk of both early and late AMD.[117] Markers of inflammation, such as C-reactive protein, may be associated with a higher risk of AMD progression.[118-120] Other possible factors that have been considered in various studies, with inconclusive findings, include hormonal status,[121-125] sunlight exposure,[126-128] alcohol use,[129-131] and vitamins B and D status.[132,133] A Cochrane systematic review in 2016 concluded that there was insufficient evidence to define a role of statins in the onset or progression of AMD.[134]

NATURAL HISTORY

Early Age-Related Macular Degeneration

As defined by the AREDS, early AMD (category 2) is characterized by small drusen (<63 μm in diameter), few medium drusen (63–125 μm in diameter), and/or minimally detected or no pigment epithelial abnormalities in the macula. Patients in this category have a low risk of progressing to advanced AMD after 5 years in either eye.[5] More recently, the AREDS study group published a report based on 10-year follow-up data obtained from approximately 85% of the originally enrolled patients.[135] In the group with a combination of small drusen or no drusen at baseline, approximately 15% developed large drusen at 10 years.

Intermediate Age-Related Macular Degeneration

Intermediate AMD (category 3) is a more critical distinction clinically because it places the individual at risk for progression to more advanced AMD. It has been defined by the AREDS as having extensive medium drusen (63–124 μm in diameter) or one or more large drusen (≥125 μm in diameter) in one or both eyes. The progression to advanced AMD at 5 years in this group is approximately 18% according to the original AREDS. However, for patients with large drusen in one eye, the rate of development of advanced AMD at 5 years is 6.3%, whereas the rate for patients with multiple bilateral large drusen increases to 26% at 5 years.[5,136] In the 10-year follow-up study of the AREDS, 37% of patients developed large drusen when medium drusen were present at baseline in one eye, and 71% developed large drusen when medium drusen were present in both eyes at baseline.[135] When medium drusen were present at baseline, 14% progressed to advanced AMD at 10 years.

In 2005, a simplified severity scale was developed for assessing AMD risk progression that is based on two primary ophthalmoscopic features: one or more large drusen (≥125 μm in diameter) and the presence of pigmentary changes.[137] Individuals with two affected eyes could then be given a five-step grading score of 0–4 (based on one point for each factor being present in each eye). The following scores enable the clinician to communicate with the patient about the approximate 5-year risk for developing advanced AMD: four factors, 45%; three factors, 26%; two factors, 9%; one factor, 4%; and zero factors, 0.5%. The approximate 10-year risks were 71%, 53%, 28%, 8%, and 1.5%, respectively.[135]

For patients without large drusen, the presence of intermediate drusen in both eyes is considered to represent one risk factor using this severity scale. Advanced AMD in one eye is counted as two risk factors. Often, the eye contralateral to the eye with Advanced AMD has large drusen and RPE pigmentary disturbances and therefore has four risk factors, the highest risk-level for progression of all patients with AMD (50% by 5 years and 71% by 10 years). Interestingly, an online AMD risk calculator that includes phenotype (simplified severity scale score described above) and demographic information (age, smoking, and family history of AMD) had excellent calibration and overall performance, whereas the addition of specific genetic analysis added little to the 9- to 10-year trend for the development of advanced AMD.[138]

Reticular pseudodrusen (also referred to as subretinal drusenoid deposits) may be under-recognized. They are best imaged using fundus autofluorescence, infrared reflectance, and/or spectral-domain optical coherence tomography (SD-OCT), and they appear to represent a meaningful risk factor associated with progression to the geographic atrophy.[139-144] (See Glossary.)

Advanced Age-Related Macular Degeneration

Advanced AMD (category 4) as defined in the AREDS refers to either neovascular AMD or geographic atrophy involving the center of the macula. Visual acuity in one eye is affected in all category 4 patients. In the Beaver Dam Eye Study, approximately 22% of the fellow eyes of such patients developed neovascular changes or geographic atrophy involving the fovea over 5 years.[145] In the AREDS, for patients with advanced AMD in one eye, the risk of progression to an advanced stage in the fellow eye ranged from 35% to 50% at 5 years, depending largely on the phenotype in the better eye.[137] In the Submacular Surgery Trial (SST), these findings were also confirmed and further emphasize the value of the simple risk scale.[146]

The phenotype of central geographic atrophy, the advanced form of non-neovascular AMD, will have one or more zones of well-demarcated RPE and/or choriocapillaris atrophy. Drusen and other pigmentary abnormalities may surround the atrophic areas. Severe VA loss occurs less commonly and more slowly in patients with geographic atrophy than in patients with neovascular AMD. Geographic atrophy involving the foveal center causes approximately 10% of all AMD-related visual loss of 20/200 or worse.[147] Patients with geographic atrophy not necessarily involving the central fovea may have relatively good distance VA yet manifest a substantially decreased ability to perform near visual tasks such as reading.[147] Doubling of the visual angle in patients with geographic atrophy has been reported to occur in as many as 50% of patients over a 2-year period.[147] Choroidal neovascularization also may occur.

Neovascular AMD is characterized angiographically as either classic, occult, predominantly classic, minimally classic, or mixed lesions. (See Glossary.) Serous and/or hemorrhagic detachment of the neurosensory retina or the RPE, and/or various stages of an elevated, fibrovascular disciform scar, may also occur.

In the Macular Photocoagulation Study (MPS), classification of neovascular AMD with CNV was based on fluorescein angiography. Classic CNV (Gass Type 2 membrane)[148-151] is defined as a well-demarcated hyperfluorescence in the early phase of the angiogram, with progressive leakage of dye into the overlying subneurosensory retinal space during the late phases of the angiogram. Occult CNV (Gass Type 1 membrane)[148-151] is characterized by either a fibrovascular pigment epithelial detachment (PED) or late leakage of undetermined source. A fibrovascular PED is an irregular elevation of the RPE that has accompanying stippled heterofluorescence or even hypofluorescence early in the angiogram, with progressive late leakage in the later stages of the angiogram. An occult lesion with late leakage of undetermined source is not elevated yet shows a similar pattern of late leakage (usually after 1 minute). Other clinical subtypes or features of neovascular AMD may include the following:

- Retinal PED
- Idiopathic PCV,[152,153] which should be suspected in patients with orange polypoid lesions and especially in patients of African or Asian descent. The lesions are often located in the

peripapillary region, but may also present in the central macula or the macular arcades initially as large hemorrhagic retinal PED, lipid exudation, and subretinal fluid. An indocyanine green (ICG) angiogram is often useful in confirming the diagnosis.

- Retinal angiomatous proliferation [154]

RATIONALE FOR TREATMENT

Prospective, randomized, controlled clinical trials support the use of antioxidant vitamins and minerals for slowing the progression to later stages of AMD, intravitreal injection of anti-VEGF agents, photodynamic therapy (PDT), and laser photocoagulation surgery to treat neovascular AMD. However, thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment (See Glossary.) At present, there is no proven therapy to prevent or treat geographic atrophy.[155]

TREATMENT MODALITIES

Early Age-Related Macular Degeneration

The use of the combination of antioxidant vitamins and minerals did not reduce the progression of early AMD to the intermediate stage of AMD, and there was insufficient power to determine the effects of the combination treatment on the progression to more advanced AMD. Therefore, there is no evidence to support the use of these supplements for patients who have less than intermediate AMD. In early AMD (AREDS category 2), only 1.3% of participants progressed to advanced AMD in 5 years. A meta-analysis by Evans in 2012 that looked at the evidence about whether to take an antioxidant vitamin or mineral supplement prevents the development of AMD concluded that there was accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD.[156]

Intermediate Age-Related Macular Degeneration

The original AREDS used a factorial design whereby 4757 participants were randomized to antioxidant vitamins, zinc, a combination of antioxidant vitamins and minerals (zinc and copper), or a placebo, and they were followed for a mean of 6 years.[5] Of these, 3640 participants were enrolled in the study for AMD. In the AREDS, daily doses of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide, to reduce the risk of zinc-induced copper deficiency anemia) were evaluated. In the AREDS2, the replacement of beta-carotene with lutein (10 mg) and zeaxanthin (2 mg) was explored, along with a lower dose (25 mg) of zinc oxide (see Table 1).

TABLE 1 ANTIOXIDANT VITAMIN AND MINERAL SUPPLEMENTS USED IN THE AREDS2

Supplement	Daily Dose*
Vitamin C	500 mg
Vitamin E	400 IU
Lutein/zeaxanthin	10 mg/2 mg
Zinc oxide	80 mg or 25 mg
Cupric oxide	2 mg

AREDS2 = Age-Related Eye Disease Study 2

SOURCE: Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report number 4. *JAMA Ophthalmol.* 2013;131(7):843–850.

* These doses are not those listed on the commercially available vitamin/mineral supplements because of a change in labeling rules by the U.S. Food and Drug Administration that specifies that the doses must reflect the amounts available at the end of the shelf life.

The AREDS2 study was a multicenter, randomized, double-masked, placebo-controlled phase III study that used a 2 x 2 factorial study design.[64] The study enrolled 4203 participants with either bilateral large drusen or large drusen in one eye and advanced disease in the fellow eye. This population represented a high-risk group for progression to more advanced stages as identified in the original AREDS.[157] Participants were randomized to receive either supplemental lutein and zeaxanthin, supplemental omega-3, or the original formulation. A secondary randomization to four variations included elimination of beta-carotene, lower zinc levels (25 mg), or both. The final results of the AREDS2 support the recommendation for substitution of beta-carotene with lutein (10 mg) and zeaxanthin (2 mg).

In the original AREDS and in AREDS2, participants who benefited from antioxidant vitamin and mineral supplementation were those who had either intermediate AMD or advanced AMD in one eye. For participants with extensive intermediate (i.e., medium-sized) drusen in one or both eyes, one or more large drusen in at least one eye, nonsubfoveal geographic atrophy in one eye, or advanced AMD (i.e., subfoveal geographic atrophy or CNV) in one eye, the rate of development of advanced AMD at 5 years was reduced by 25% in the participants using the combination treatment of antioxidant vitamins with zinc and copper. The risk of losing vision of 3 or more lines (doubling of the visual angle) was reduced by 19% with this combination treatment. Although zinc alone or antioxidants alone reduced progression, the therapy that resulted in a statistically significant reduction in both the development of advanced AMD and vision loss was the combination treatment of antioxidant vitamins and minerals (Table 2).

TABLE 2 SUMMARY OF RESULTS OF THE ORIGINAL AREDS FOR DEVELOPING ADVANCED AGE-RELATED MACULAR DEGENERATION AND VISION LOSS

	Antioxidants Plus Zinc	Zinc Alone	Antioxidants Alone
Reduction of the relative risk of developing advanced AMD	25%	21%	17%
Reduction of the relative risk of vision loss (3 or more lines)	19%	11%	10%

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study

SOURCE: 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 number 8. *Arch Ophthalmol*. 2001;119(10):1417–1436.

A meta-analysis by Evans in 2017 concluded that individuals with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation.[158] This finding is drawn from one large trial conducted in a relatively well-nourished American population. The generalizability of these findings to other populations is not known. Although generally regarded as safe, vitamin supplements may have side effects.[65] Evans also published a second meta-analysis concluding that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. The same probably applies to vitamin C and the multivitamin (Centrum Silver) investigated in the one trial reported to date. There is no evidence with respect to other antioxidant supplements, such as lutein and zeaxanthin.[158] A meta-analysis of the adverse effects of nutritional supplementation reported that there is an increased risk of death from vitamin A, beta-carotene, and vitamin E supplements (16%, 7%, 4%, respectively), but not from vitamin C supplements.[159] Other investigators have raised concerns about the methodology for this meta-analysis. There is potential bias in the analyses owing to the omission of clinical trials that had no deaths and the lack of biological plausibility in the authors' interpretation of the results of the subgroup analyses.[160-162] Also a number of studies in the meta-analysis used antioxidant dosages much higher than those used in the AREDS and did not find an adverse association of high-dose antioxidant supplementation.[163] Of great concern, two studies reported an increased mortality among patients who were heavy smokers and were also taking beta-carotene supplements to prevent lung cancer.[164,165]

The AREDS2 study results demonstrated that in patients at high risk for progression, there was no statistically significant difference associated with supplementation with the original AREDS formula versus each of the other modifications on AMD progression. As mentioned earlier, the addition of omega-3 supplementation (DHA and EPA) had no further benefit. This

result was also suggested by a meta-analysis by Chong et al in 2008. [73] Subgroup analysis indicated that for those in the lowest quartile for lutein and zeaxanthin intake, supplemental lutein and zeaxanthin was protective (95% CI, 0.59–0.94; *P*=0.01). The authors concluded from all available evidence that lutein and zeaxanthin represent an appropriate substitute for beta-carotene in the supplement.[64] Finally, there was no demonstrated detrimental effect of lowering the zinc levels (25 mg) on progression to advanced disease.[64] A meta-analysis by Vishwanathan in 2013 did show that zinc supplementation alone may not be sufficient to produce clinically meaningful changes in VA.[166]

Neovascular Age-Related Macular Degeneration

With the introduction of the VEGF inhibitors pegaptanib sodium (Macugen®, Eyetech, Inc., Cedar Knolls, NJ) in 2004, off-label bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) in 2005, ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA) in 2006, and aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) in 2011, more effective treatments for neovascular AMD exist. The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies. Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD and a Cochrane systematic review demonstrates the effectiveness of these agents to maintain visual acuity.[167] *(I+, Good quality, Strong recommendation)*

Aflibercept is a pan–VEGF-A and placental growth factor (PGF) blocker approved by the US Food and Drug Administration (FDA) that has been documented to be of similar efficacy to ranibizumab in the head-to-head phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials.[168] In these pivotal studies, the currently approved 2-mg dose of aflibercept was administered by intravitreal injection every 4 weeks and every 8 weeks after three monthly loading doses. In the first year, both study arms were similar to 0.5-mg ranibizumab dosed every 4 weeks.

Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF. It is FDA approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer. Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab.[169,170] Because preliminary reports appeared favorable, ophthalmologists began to use intravitreal bevacizumab off-label to treat CNV. Comparative trials and uncontrolled case series reported improvements in VA and decreased retinal thickness by optical coherence tomography (OCT) following intravitreal bevacizumab treatment.[171-177] Informed consent information is available on the benefits and risks of intravitreal bevacizumab and its off-label status.[178]

Intravitreal ranibizumab (0.5 mg) is FDA approved for the treatment of all subtypes of neovascular AMD, based on results from three double-masked, randomized controlled trials.[179,180] (See Table 3.) Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment developed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of all isoforms of human VEGF-A.

1

TABLE 3 EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
ANCHOR (2006; ranibizumab injection)[180]	423	Mean age 77 years; BCVA 20/40 to 20/320; total lesion size ≤5400 µm; no previous treatment (including verteporfin therapy) that might compromise an assessment of the study treatment; predominantly classic CNV lesions	Monthly ranibizumab injections for 2 years	10% (0.5 mg)	41% (0.5 mg)	N/A (All patients received treatment)		2
			Verteporfin PDT on day 0 and then PRN following FA at months 3, 6, 9, or 12	66%	6%			
MARINA (2006; ranibizumab injection)[179]	716	Mean age 77 years; BCVA 20/40 to 20/320; primary or recurrent CNV; minimally classic or occult with no classic CNV lesions; presumed recent progression of disease	Monthly ranibizumab injections for 2 years	10% (0.5 mg)	33% (0.5 mg)	47%	4%	2
VIEW 1 and 2 (2012; aflibercept injection)[168]	2419	Mean age 76 years; BCVA 20/40 to 20/320; primary, active subfoveal (or juxtafoveal) CNV, with the total CNV area (classic plus occult CNV) ≥50% of total lesion size; any lesion subtype	Aflibercept 0.5 mg q 4 weeks 4	4%	30%	NA (All patients received treatment)		1
				5%	34%			
			Aflibercept 2.0 mg q 4 weeks	4%	31%			
			Aflibercept 2.0 mg q 4 weeks x 3, then q 8 weeks	6%	33%			
			Ranibizumab 0.5 mg q 4 weeks					

TABLE 3 EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CNV (CONTINUED)

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
CATT (2011; bevacizumab vs ranibizumab injection)[174]	1208	Mean age 79 years; BCVA 20/25 to 20/320; untreated, active CNV, with CNV, fluid, or hemorrhage under the fovea	Ranibizumab 0.5 mg q 4 weeks Bevacizumab 1.25 mg q 4 weeks Ranibizumab 0.5 mg PRN Bevacizumab 1.25 mg PRN	6% 6% 5% 9%	34% 31% 25% 28%	NA (All patients received treatment)	1	CATT (bevacizumab vs. ranibizumab injection)[174]
VISION (2006; pegaptanib sodium injection)[181]	590	Age ≥50 years; BCVA 20/40 to 20/320; subfoveal CNV with total lesion size ≤12 disc areas; IOP ≤23 mmHg	Injection every 6 weeks for 54 weeks (9 total treatments); then rerandomized and injection every 6 weeks through week 96 (8 total treatments)	45%	10%	59%	4%	2
TAP (2001; verteporfin PDT)[182]	609	Mean age 75 years; BCVA 20/40 to 20/200; classic CNV or occult CNV if >50% of total lesion size	Following first treatment, retreatment was considered every 3 months per FA findings through 21 months of follow-up	47% 41%‡	8%	62% 69%†	4%	2

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; FA = fluorescein angiography; CATT = Comparison of Age-Related Macular Degeneration Treatment Trials; IOP = intraocular pressure; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; NA = not applicable; PRN = as needed; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISION = VEGF Inhibition Study in Ocular Neovascularization

* Defined as doubling of the visual angle.

† Pegaptanib sodium injection was administered to patients who were allowed both prior and on-study PDT.

‡ Predominantly classic.

The Comparison of AMD Treatment Trials (CATT) was a multicenter clinical trial that compared the safety and effectiveness of bevacizumab with ranibizumab and an individualized dosing regimen (as needed, or PRN) with monthly injections. At 1 year, the CATT study found that ranibizumab and bevacizumab had comparable equivalence VA improvements for monthly dosing.[174] Ranibizumab PRN had similar VA improvements compared with a fixed schedule of monthly injections. Further follow-up at 2 years showed that the two drugs remained comparable in both efficacy and safety, but the PRN arms together did not perform as well in terms of maintaining the visual gains at the end of year 1 compared with the two monthly arms, especially in the bevacizumab PRN group.[183] The CATT 5-year follow-up study demonstrated vision gains during the first 2 years that were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti-VEGF therapy as a major long-term therapeutic advance for neovascular AMD.[184] Similar results were seen in the 2-year Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial conducted in the United Kingdom.[185,186] (See Glossary.) Presently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab.[184] A meta-analysis by Nguyen in 2018 of over 8,000 eyes comparing all three drugs concluded that bevacizumab and ranibizumab had equivalent efficacy for best-corrected visual acuity (BCVA), whereas ranibizumab had greater reduction in central macular thickness, and aflibercept and ranibizumab had comparable efficacy for BCVA and central macular thickness.[187] The review by Chen in 2015 also elicited similar results.[188] The systemic safety data in the CATT and IVAN studies are inconclusive and two Cochrane systematic reviews have also concluded that if a difference in safety between these anti-VEGF drugs exists, it is minimal.[189,190] *(I+, Good quality, Strong recommendation)* A real world analysis of 13,859 patients found that all three agents improved visual acuity similarly over 1 year.[191]

Pegaptanib sodium is a selective VEGF antagonist that binds to the 165 isoform of VEGF-A. It was the first anti-VEGF agent available for treating neovascular AMD. Pegaptanib sodium injection is FDA approved for the treatment of all subtypes of neovascular AMD, with a recommended dosage of 0.3 mg injected every 6 weeks into the vitreous. These recommendations were based on results from two double-masked, randomized controlled trials.[181] (See Table 3.) Unlike the other anti-VEGF agents that are currently available (ranibizumab, aflibercept, and bevacizumab), pegaptanib treatment does not improve VA on average in patients with new-onset neovascular AMD and is rarely used in current clinical practice.

Randomized clinical trials have been performed to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin

PDT, following the publication of results from uncontrolled case series.[192-195] However, the data do not currently support the use of combination therapy with steroids, especially given the long-term side effects of glaucoma and cataract that are associated with corticosteroid use.

The DENALI and MONT BLANC studies (ranibizumab and verteporfin PDT compared with ranibizumab alone) did not show a significant benefit of adding PDT to anti-VEGF therapy in new-onset neovascular AMD.[196,197] (See Glossary.) However, the EVEREST study demonstrated that fewer anti-VEGF injections were needed in combination therapy compared with anti-VEGF monotherapy in eyes with the PCV variant of neovascular AMD.[198] A 2017 meta-analysis and systematic review also concluded that treatment of PCV by PDT combined with ranibizumab is valuable in improving VA and maintaining long-term effectiveness but recommended further study.[199,200] A randomized trial of 310 subjects has shown aflibercept to effectively treat PCV in 85% of patients; 15% required PDT for control.[200] A 2018 meta-analysis of 16 studies by Gao et al compared 587 patients in the monotherapy group with various anti-VEGF agents against 673 patients in the combination group and found no statistically significant difference between groups in mean BCVA, the proportion of patients who gained 15 or more letters, or central retinal thickness at the end of the study.[201] However, combination therapy did require fewer anti-VEGF injections, as noted in other studies with reduced-fluence PDT demonstrating this reduction in number of injections at a statistically significant level as opposed to the standard fluence group.[201]

Subfoveal Choroidal Neovascularization

In addition to intravitreal injections of VEGF inhibitors, verteporfin PDT and thermal laser photocoagulation surgery remain approved options for the treatment of subfoveal lesions. Current practice patterns support the use of anti-VEGF monotherapy for patients with newly diagnosed neovascular AMD and suggest that these other therapies are rarely needed. Photodynamic therapy with verteporfin has FDA approval for the treatment of AMD-related, predominantly classic, subfoveal CNV; treatment trial results are described in Table 3. The efficacy of thermal laser photocoagulation surgery for CNV was studied in the MPS (early 1990s) in a randomized, controlled, multicenter trial.[148-151] The MPS directly treated eyes that had subfoveal lesions using thermal laser surgery,[150] but the outcomes were poor and do not compare with the positive VA benefits found with current anti-VEGF therapy. Thus, thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment.

Table 3 (at the end of this section) summarizes the findings from randomized controlled trials of verteporfin PDT and VEGF inhibitors for the treatment of subfoveal CNV. The

entry criteria varied among these studies and may have contributed to the differences among treatment cohorts.

Juxtafoveal Choroidal Neovascularization

Although randomized, controlled clinical trials have not routinely included patients with juxtafoveal CNV, many clinicians extrapolated the data from current trials to consider intravitreal injections of anti-VEGF agent as the primary therapy for juxtafoveal lesions.

In the MPS, treatment of well-demarcated juxtafoveal CNV lesions resulted in a small overall treatment benefit.[151] The rates of "persistence" (CNV leakage within 6 weeks of laser photocoagulation surgery) and "recurrence" (CNV leakage more than 6 weeks after laser photocoagulation surgery) were high (80%) at 5 years. After 5 years of follow-up, 52% of eyes treated for juxtafoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 61% of untreated eyes.[151]

Extrafoveal Choroidal Neovascularization

There still remains a possible role for thermal laser surgery treatment in eyes with extrafoveal and peripapillary CNV lesions as defined by the MPS.[148,202] Although photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a substantial reduction in the risk of severe visual loss for the first 2 years, recurrence or persistence occurs in approximately 50% of cases, thus reducing this benefit over the subsequent 3 years of follow-up.[148] After 5 years of follow-up, 48% of eyes treated for extrafoveal lesions progressed to VA loss of 30 or more letters when compared with 62% of untreated eyes.[148] The historical data are important to recognize in current practice patterns, as none of the anti-VEGF or PDT trials included extrafoveal lesions. Practitioners have extrapolated and applied data from the dramatic improvements seen in the treatment of subfoveal lesions to extrafoveal lesions. The current trend is to use anti-VEGF agents in preference to laser photocoagulation surgery. Laser surgery for extrafoveal lesions remains a less commonly used, yet reasonable, therapy. Current therapies that have insufficient data to demonstrate clinical efficacy include radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal corticosteroids with verteporfin PDT. Therefore, at this time, these therapies are not recommended.

CARE PROCESS

PATIENT OUTCOME CRITERIA

Patient outcome criteria are to reverse or minimize visual loss and improve visual function.

DIAGNOSIS

The initial evaluation of a patient with signs and symptoms suggestive of AMD includes all features of the comprehensive adult medical eye evaluation,[203] with particular attention to those aspects relevant to AMD.

History

An initial history should consider the following elements:

- Symptoms[204]
  - Metamorphopsia
  - Decreased vision
  - Scotoma
  - Photopsia
  - Difficulties in dark adaptation
- Medication and nutritional supplement use
- Ocular history[11,205,206]
- Medical history[11,205,206] (including any hypersensitivity reactions[181,207])
- Family history, especially family history of AMD[85,208]
- Social history, especially a quantitative smoking history [39-43]

Examination

- Comprehensive eye examination
- Amsler grid
- Stereoscopic biomicroscopic examination of the macula

Binocular slit-lamp biomicroscopy of the ocular fundus is often necessary to detect subtle clinical signs of CNV. These include small areas of hemorrhage, hard exudates, subretinal fluid, macular edema, subretinal fibrosis, or pigment epithelial elevation.

Diagnostic Tests

Optical Coherence Tomography

Optical coherence tomography is important in diagnosing and managing AMD, particularly with respect to determining the presence of subretinal and intraretinal fluid and in documenting the degree of retinal thickening.[209] Optical coherence tomography defines the cross-sectional architecture of the retina, which is not possible with any other imaging technology. It may reveal the presence of fluid that is not apparent on biomicroscopy alone. It also helps in evaluating the response of the retina and RPE to therapy by allowing structural changes to be followed accurately.[210-213] Newer-generation OCT modalities, including SD-OCT, are preferred technologies. Advances in OCT have increased the image resolution and enhanced our ability to detect structural changes of the retina and choroid.[214-217] The implementation of newer technologies, such as swept-source OCT (that is FDA approved), is evolving at this time.[215-217]

Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCTA) is a newer imaging modality that provides noninvasive evaluation of the retinal and choroidal vasculature and is becoming more commonly applied in the evaluation and management of AMD, but it has not replaced other angiographic methods.[218]

Fluorescein Angiography

Intravenous fundus fluorescein angiography is indicated[148,150,151] when the patient complains of new metamorphopsia or has unexplained blurred vision, and/or when clinical examination reveals elevation of the RPE or retina, macular edema, subretinal blood, hard exudates, or subretinal fibrosis, or the OCT shows evidence of fluid. Fluorescein angiography is also warranted as follows:

- To detect the presence of and determine the extent, type, size, and location of CNV. If verteporfin PDT or laser photocoagulation surgery is being considered, the angiogram is used as a guide to direct treatment. The role and indications for fluorescein angiography are evolving as continued advances in OCT occur.
- To detect persistent or recurrent CNV or other retinal diseases following treatment. (See Glossary.)
- To assist in determining the cause of visual loss that is not explained by the clinical examination.

If CNV is suspected on the basis of new symptoms or ocular findings, fluorescein angiography should be performed and interpreted expeditiously by an individual experienced in managing patients with neovascular AMD.[148,150,151]

When fluorescein angiography is performed, the physician must be aware of potential risks associated with this procedure:[219,220] tissue infiltration (if the drug extravasates the vein), pain, and allergic reactions. Even death from anaphylaxis has been reported (approximately 1 in 200,000 patients). Each angiographic facility should have a care plan in place for an emergency situation as well as a clear protocol to minimize the risks and to manage complications.

Fundus Photography

Color fundus photographs may be obtained when angiography is performed, because they are useful in finding landmarks, evaluating serous detachments of the neurosensory retina and RPE, and determining the etiology of blocked fluorescence. Fundus photographs may also be used as a baseline reference for selected patients with advanced non-neovascular AMD and for follow-up of treated patients.

Fundus Autofluorescence

Fundus autofluorescence is helpful to demonstrate areas of geographic atrophy and monitor their progression. Some patterns of autofluorescence may predict faster rates of geographic atrophy.[221] Also, fundus autofluorescence may be used to quantify lipofuscin in the RPE.[221]

Indocyanine Green Angiography

Indocyanine green angiography is a technique that allows visualization of the choroidal circulation. The value of this test in evaluating and treating AMD has been debated.[222] Indocyanine green angiography has been shown to be useful in evaluating specific forms of AMD, such as PED, poorly defined CNV, occult CNV, and lesions including retinal angiomatous proliferation or idiopathic PCV.[154,223] The PCV form of neovascular AMD may be more easily identified when ICG is used, particularly in patients of African or Asian descent.[12,224] When ICG angiography is performed, the physician must be aware of potential risks associated with this procedure: severe medical complications, allergic reactions, and even death.[225]

Other Tests

Several other tests including microperimetry[226] (to measure macular sensitivity), and adaptive optics (to identify individual rods and cones)[227] have been used to evaluate patients with AMD; however, their specific role in clinical practice has yet to be specifically defined.

MANAGEMENT

Consequences of untreated neovascular macular degeneration include a substantial economic burden on patients, their family and society. Anti-VEGF agents are cost-effective for management of neovascular macular degeneration. Choice of the anti-VEGF agent to use should be individually tailored based on discussion between the patient and physician. Early detection and treatment of AMD to arrest the deterioration in vision may help preserve patients' quality of life and independence. Management options for AMD include observation, antioxidant vitamin and mineral supplements, intravitreal injection of anti-VEGF agents, PDT, and laser photocoagulation surgery. Several new treatments such as stem cells and gene therapy are currently under investigation.[228-230]

Patients who are currently smoking should be advised to stop.[231,232] Studies have found that the physician's advice to stop smoking is a helpful motivator for patients who are attempting to quit[231] and is associated with increased long-term smoking abstinence rates.[232] An important component of care for an AMD patient is referral for vision rehabilitation as well as continued follow-up for general eye care.

Monitoring and Early Detection

Patients with early AMD and/or a family history of AMD should be encouraged to assess their own VA using monocular vision testing (i.e., Amsler grid or electronic home monitoring[233,234]) and have scheduled dilated eye examinations for detecting the intermediate stage of AMD. (See Glossary.) Treatment with antioxidants and minerals as described previously in the original AREDS and AREDS2 trials should be considered for patients who have progressed to intermediate or advanced AMD in at least one eye.

Patients with a high-risk AMD phenotype are at increased risk of progression to advanced AMD and should be educated about methods of detecting new symptoms of CNV, including self-monitoring. They should also be educated about the need for promptly reporting new symptoms to an ophthalmologist who can confirm if the new symptoms are from CNV and who can begin any necessary treatment.

Follow-up examinations of patients at increased risk of progression to advanced AMD may enable (1) early detection of asymptomatic and treatable neovascular lesions that could improve or preserve VA, (2) education about the possible benefit of AREDS2-based nutritional supplements, and (3) reinforcement of the need for self-monitoring and prompt evaluation with the onset of new symptoms. Patients who check monocular near vision (reading/Amsler grid/Amsler-grid equivalent) may be more likely to become aware of subtle visual symptoms due to CNV, increasing the likelihood of detecting CNV at an early stage which, on average, yields better long-term visual outcomes with treatment compared with neovascular disease detected at a more advanced stage.

Sensitivity and specificity for CNV detection with en face OCTA combined with cross-sectional OCTA approaches that of the gold standard of fluorescein angiography with OCT, and it is better than *en face* OCTA alone.[235] Structural OCT alone has excellent sensitivity for CNV detection. False positives from the structural OCT can be mitigated with the addition of flow information with OCTA.[235] Optical coherence tomography angiography may detect subclinical CNV, which needs close monitoring and not treatment.[179,218,236,237] Electronic monitoring devices are now available to aid in the detection of neovascularization at an early stage. Such devices use hyperacuity perimetry (or vernier acuity) to create a quantified central visual map of metamorphopsia.[238] Further studies of a variety of such devices are ongoing.

Indications for Treatment for Choroidal Neovascularization

Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4. The criteria for treatment of AMD and the techniques of therapy are described in the aflibercept, bevacizumab, ranibizumab, pegaptanib, MPS, and AREDS literature. Aflibercept, ranibizumab, and pegaptanib-injection product labeling and other literature discuss techniques of intravitreal injection.[181,207,239-241] Recently, conbercept has shown promising results in the management of wet AMD,[242] although it has yet to receive FDA approval for its use. Similarly, abicipar has completed phase II clinical trials and has shown an extended duration of effect with a good safety profile; however, it has not received FDA approval. [243,244] Recently reported results from the HAWK and HARRIER phase III clinical trials showed that brolucizumab achieved its primary endpoint of noninferiority of BCVA change compared with aflibercept at week 48. Patients treated with brolucizumab achieved superior reductions in central subfield thickness compared with aflibercept. Fewer patients treated with brolucizumab had sub-retinal fluid, inter-retinal fluid, and sub-RPE fluid. Brolucizumab is currently awaiting FDA approval.[245]

As is the case with most clinical trials, these treatment trials do not provide clear guidance for the management of all patients encountered in clinical practice. To date, the major prospective randomized anti-VEGF treatment trials (Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD [ANCHOR], Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA], VIEW, CATT, IVAN, HARBOR) used either a fixed continuous treatment regimen (approximately every 4 or 8 weeks) or an individualized discontinuous treatment regimen (PRN).[168,174,179,180,183,185,186,246]

TABLE 4 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AGE-RELATED MACULAR DEGENERATION

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations	
Non-neovascular AMD		**Intervals**	**Testing**
Observation with no medical or surgical therapies[5,145,247]	Early AMD (AREDS category 2)	Return examination at 6–24 months if asymptomatic or prompt examination for new symptoms suggestive of CNV	Fundus photos, fluorescein angiography, OCT, or OCTA as appropriate[5]
	Advanced AMD with bilateral subfoveal geographic atrophy or disciform scars	Return examination at 6–24 months if asymptomatic or prompt examination for new symptoms suggestive of CNV	Fundus photos, fluorescein angiography, OCT, or OCTA as appropriate[5]
Antioxidant vitamin and mineral supplements as recommended in the original AREDS and AREDS2 reports[5,18]	• Intermediate AMD (AREDS category 3) • Advanced AMD in one eye (AREDS category 4)	Return examination at 6–18 months if asymptomatic or prompt examination for new symptoms suggestive of CNV	• Monitoring of monocular near vision (reading/Amsler grid) • Fundus photography and/or fundus autofluorescence as appropriate • Fluorescein angiography and/or OCT for suspicion of CNV
Neovascular AMD			
Aflibercept intravitreal injection 2.0 mg as described in published reports[168]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist. A maintenance treatment regimen of every 8 weeks has been shown to have results comparable to every 4 weeks in the first year of therapy. • Monitoring of monocular near vision (reading/Amsler grid)	
Bevacizumab intravitreal injection 1.25 mg as described in published reports[172-177,183,185,240,248] The ophthalmologist should provide appropriate informed consent with respect to the off-label status.[178]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters. • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)	
Ranibizumab intravitreal injection 0.5 mg as recommended in literature[174,179,180,183,185,207,246,249-251]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.[207] • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)	

TABLE 4 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AMD (CONTINUED)

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations
Less Commonly Used Treatments for Neovascular AMD		
PDT with verteporfin as recommended in the TAP and VIP reports[182,252-254]*	• Macular CNV, new or recurrent, where the classic component is >50% of the lesion and the entire lesion is ≤5400 µm in greatest linear diameter • Occult CNV may be considered for PDT with vision <20/50 or if the CNV is <4 MPS disc areas in size when the vision is >20/50 • Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases	• Return examination approximately every 3 months until stable, with retreatments as indicated • Monitoring of monocular near vision (reading/Amsler grid)
Thermal laser photocoagulation surgery as recommended in the MPS reports is rarely used[148,151,247]	• May be considered for extrafoveal classic CNV, new or recurrent • May be considered for juxtapapillary CNV	• Return examination with fluorescein angiography approximately 2–4 weeks after treatment, and then at 4–6 weeks and thereafter depending on the clinical and angiographic findings • Retreatments as indicated • Monitoring of monocular near vision (reading/Amsler grid)

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy

* Contraindicated in patients with porphyria or known allergy.

The PRN regimens using ranibizumab appear to have efficacy and safety comparable to fixed monthly regimens over 1 year of treatment, but they do not maintain the initial visual gains with longer follow-up.[183,255] Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens and other PRN anti-VEGF regimens.[183] Vision gains during the first 2 years of the CATT clinical trials were not maintained at the 5-year follow-up visit, but 50% of the patients maintained a VA of 20/40.[184] A continuous, variable dosing regimen that attempts to individualize therapy, commonly referred to as "treat and extend," is frequently used in clinical practice as an alternative to the two treatment approaches above.[248-251] Prospective studies such as Lucentis Compared to Avastin Study (LUCAS) have shown similar efficacy between monthly and treat-and-extend for bevacizumab and ranibizumab.[256]

Subretinal hemorrhages are relatively common in neovascular AMD. Small subretinal hemorrhages are a sign of active CNV or PCV and may be managed with anti-VEGF therapy. For the management of larger submacular hemorrhages, the SST study was inconclusive. Pneumatic displacement procedures, the use of tPA, and/or pars plana vitrectomy have been proposed. The data on management of these larger hemorrhages are inadequate to make a recommendation at this time.[257]

The risks, benefits, and complications of the treatment and the alternatives to it should be discussed with the patient and informed should be consent obtained.[146,258]

Complications of Treatment

Possible complications of the four main modalities of treatment for AMD are listed below. Retinal pigment epithelium rips (tears) may occur with or without these treatment modalities, yet this is not a contraindication to continued anti-VEGF therapy.

Intravitreal Pharmacotherapy

All anti-VEGF treatments may carry theoretical risks for systemic arterial thromboembolic events and increased intraocular pressure, although the results of clinical trials studying these risks remain inconclusive.[259-262] A recent review of the literature concluded that anti-VEGF therapy is safe and effective for neovascular AMD.[263] The risks of intravitreal anti-VEGF agents in pregnant or lactating women have not been studied.[264,265] Intravitreal pharmacotherapy can result in endophthalmitis, noninfectious inflammation, retinal tear, or detachment.

- Aflibercept injection
  - Endophthalmitis (cumulative ≤1.0% over 1 year in VIEW studies)[168]

At 1 year, there were no statistically significant differences in rates of serious systemic adverse events such as death, arteriothrombotic events, or venous thrombotic events between ranibizumab and aflibercept.[168,266]

- Bevacizumab injection
  - Reported safety data are limited by relatively short and variable follow-up periods and by differences in reporting criteria.[267,268]
  - Reported ocular adverse events include bacterial endophthalmitis per injection (0.16%), tractional retinal detachments (0.16%), uveitis (0.09%), rhegmatogenous retinal detachment (0.02%), and vitreous hemorrhage (0.16%).[240,269]

The CATT study had limited statistical power to identify any differences in treatment-related adverse events between bevacizumab and ranibizumab. At 1 year, there were no statistically significant differences in rates of death, arteriothrombotic events, or venous thrombotic events for the two drugs. There was a higher rate of serious systemic events (e.g., arteriothrombotic events, venous thrombosis, or gastrointestinal disorders such as hemorrhage) among patients treated with bevacizumab compared with ranibizumab (24% vs. 19%; P=0.04), and this statistically significant difference was persistent at 2 years of follow-up.[174,183] The IVAN trial showed greater serum VEGF suppression with bevacizumab but did not show any statistically significant difference in serious systemic adverse events.[185]

- Ranibizumab injection
  - Endophthalmitis (cumulative ≤1.0% over 2 years in MARINA study; <1.0% over 1 year in ANCHOR study)
  - Retinal detachment or traumatic injury to the lens (<0.1% of treated cases during the first year of treatment)[179,180]
- Pegaptanib sodium injection[270]
  - Endophthalmitis (1.3% of treated cases during the first year of treatment)
  - Traumatic injury to the lens (0.6% of treated cases during the first year of treatment)
  - Retinal detachment (0.7% of treated cases during the first year of treatment)
  - Anaphylaxis/anaphylactoid reactions including angioedema (rare; these were reported following FDA approval)

Verteporfin Photodynamic Therapy

- A severe decrease in central vision occurred within 1 week following treatment in 1% to 4% of patients, and may be permanent[182,252,253]
- Infusion site extravasation
- Idiosyncratic back pain during infusion of the drug (1%–2% of patients)[182,252,253]

- Photosensitivity reaction (<3% of patients).[182,252,253] The stated, current recommendations are to avoid direct sunlight for the first 5 days after a treatment.

Verteporfin is contraindicated in patients with porphyria or a known allergy or sensitivity to the drug. Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breastfeeding, or of pediatric age, because these patients were not studied in published reports.

Thermal Laser Photocoagulation Surgery

- Severe vision loss following treatment, which may be permanent
- Rupture of Bruch's membrane with subretinal or vitreous hemorrhage
- Effects on the fovea in subfoveal or juxtafoveal CNV

Thermal laser is no longer recommended for subfoveal CNV. Introduction or enlargement of a pre-existing scotoma, with or without VA loss, is not a complication of thermal laser photocoagulation surgery; rather, it is an anticipated side effect of the treatment. Similarly, recurrence or persistence of CNV, or the development of new CNV and further visual deterioration after adequate thermal laser surgery, is usually a result of the disease process and is not a complication. These realities must be emphasized to the patient and family before treatment.

Supplements of High-Dose Antioxidants and Zinc

- Beta-carotene
  - Self-reported yellowing of the skin (8.3% in the antioxidant arm compared with 6.0% in the no antioxidant arm; P=0.008)[5]
  - Increased risk of developing lung cancer in current smokers (an excess cumulative incidence of lung cancer was observed after18 months and increased progressively thereafter, resulting in an 18% difference in incidence by the end of the study (95% CI, 3%–36%; P=0.01) between the patients who received beta-carotene and those who did not).[164] The active treatment group had a relative risk of lung cancer of 1.28 (95% CI, 1.04–1.57; P=0.02), as compared with the placebo group.[165]
- Zinc
  - Increased risk of hospitalizations for genitourinary causes, i.e., unspecified urinary tract infection and prostatic hyperplasia in men and stress incontinence in women (7.5% in those treated with zinc compared with 4.9% in those not treated with 80 mg of zinc; P=0.001).[5] In the AREDS2, there was no significant difference in AMD progression between 80 mg and 25 mg of zinc.
  - Copper-deficiency anemia (concomitant administration of copper is necessary; included in the AREDS and AREDS2)

When considering long-term supplementation, some people may have reason to avoid one or more of the supplements evaluated in the original AREDS or AREDS2. Because of the potential adverse effects, such as increased rate of genitourinary conditions that may require hospitalizations, the high doses of antioxidant vitamins and minerals recommended by the original AREDS and AREDS2 should be reviewed by the patient's primary care physician.

Follow-up Evaluation

A history and examination are the recommended elements of the follow-up visits. Recommended follow-up intervals are listed in Table 4.

History

The follow-up history should take into account the following:

- Symptoms, including decreased vision and metamorphopsia[204]
- Changes in medications and nutritional supplements
- Changes in medical and ocular history[11,205,206]
- Changes in social history (smoking)[39-43]

Examination

The examination on the follow-up visit should include the following:

- VA at distance with correction
- Amsler grid
- Stereoscopic biomicroscopic examination of the fundus

Follow-up after Treatment for Neovascular Age-Related Macular Degeneration

In addition to the above recommendations, patients who have been treated with aflibercept, bevacizumab, ranibizumab, or pegaptanib sodium injection; verteporfin PDT; or thermal laser photocoagulation surgery should be examined at regular intervals by means of biomicroscopy of the fundus. Optical coherence tomography,[209] OCTA,[271-274] fluorescein angiography,[148,150,151] and fundus photography may be helpful to detect signs of active exudation or disease progression and should be used when clinically indicated. In common clinical practice, OCT is a simple, noninvasive procedure that is well accepted by the patient and provides important information for the provider to manage AMD.

Initial treatment and follow-up with intravitreal anti-VEGF therapy (aflibercept, bevacizumab and ranibizumab) should be at approximately 4-week intervals.[168,179,183] Subsequent follow-up and treatment intervals vary depending on the clinical findings and judgment of the treating ophthalmologist. After three loading doses administered at 4 week

intervals, a maintenance treatment regimen every 8 weeks with aflibercept has been shown to have comparable efficacy to every 4 weeks of either ranibizumab and aflibercept in the first year of therapy.[168] There is no consensus about the ideal treatment intervals with anti-VEGF agents. There are three protocols: monthly or bimonthly injections, treat-and-extend, or PRN. A minority of retina specialists will treat patients monthly. Treat-and-extend is based on anti-VEGF injection following an interval based on treatment response. As-needed treatment is based on the presence or absence of subretinal or intraretinal fluid. The few patients currently being treated with pegaptanib sodium injection should have follow-up examinations approximately 6 weeks after each injection.

Subsequent examinations, OCT, OCTA, and fluorescein angiography should be performed as indicated depending on the clinical findings and the judgment of the treating ophthalmologist. Treated patients should be instructed to report symptoms of endophthalmitis, retinal detachment, or decreased vision, and they should be re-examined promptly.

Fellow Eyes without Choroidal Neovascularization

For patients with unilateral disease, the fellow eye without CNV remains at high risk of developing advanced AMD.[275] The risk can be lowered by as much as 36% over a 10-year period by taking the AREDS/AREDS2 supplements.[5] Patients should be instructed to monitor their vision and to return to the ophthalmologist periodically, even in the absence of symptoms, but promptly after the onset of any new or significant visual symptoms. Patients at exceptionally high risk (e.g., the presence of advanced AMD in one eye and large drusen with RPE changes in the fellow eye) may be examined more frequently (i.e., every 6–12 months) in an effort to detect asymptomatic CNV at a treatable stage. Since some patients with AMD also have cognitive impairment, a family member or care assistant should prompt the patient to self-test. Optical coherence tomography is useful and OCTA may be useful for evaluating the status of high-risk fellow eyes.

PROVIDER AND SETTING

Ancillary clinical personnel should be aware that patients with the onset of new symptoms suggestive of AMD (e.g., new visual loss, metamorphopsia, or scotoma) should be examined promptly. The ophthalmologist will perform most of the examination and all treatment, and certain aspects of the testing may be conducted by other trained individuals under the ophthalmologist's supervision.

COUNSELING AND REFERRAL

All patients with AMD should be educated about the prognosis of the disease and the potential value of treatment as appropriate for their visual and functional status. Patients can be informed that while central visual loss is common, total visual loss is extremely rare. Patients with AMD can be reassured

that there is no harm in using their eyes for normal visual tasks, and they may be told that the effect of total sunlight exposure remains uncertain. Insofar as cigarette smoking is a key modifiable risk factor, smoking cessation is strongly recommended when advising patients with AMD or at risk for AMD.

The informed consent process should include a discussion of the risks and benefits of treatment and treatment alternatives. The off-label status of bevacizumab for neovascular AMD should be included in the discussion; information and a consent form are available from the Ophthalmic Mutual Insurance Company.[178]

Vision rehabilitation optimizes the patient's functional ability,[276] and patients with reduced visual function should be referred for vision rehabilitation and social services.[277] Patients with severe visual loss related to AMD who are referred for vision rehabilitation services often have unrealistic expectations. Educating patients that the visual rehabilitation specialist helps to optimize their existing visual function, rather than "helping them see better" will establish more appropriate expectations around such services. Special optical or electronic magnifying lenses, bright lights, and electronic reading aids may help patients to read more effectively, but not as well as they did before the onset of AMD. An Implantable Miniature Telescope (IMT) is an FDA-approved device that may be effective for screened, phakic, motivated patients with end-stage AMD, and it appears to be cost-effective.[278,279] A systematic review in 2018 found insufficient evidence on the IMT's safety and effectiveness in patients with late or advanced AMD.[267] More information on vision rehabilitation, including materials for patients, is available at www.aao.org/smart-sight-low-vision.

Loss of VA increases the risk of frequent falls.[280,281] Depression and visual hallucinations (Charles Bonnet syndrome) frequently accompany severe central vision loss. Patients who have Charles Bonnet syndrome and their family members should be informed that visual symptoms are not unusual and do not represent a sign of psychosis or mental deterioration. The ophthalmologist may inquire about symptoms of clinical depression and, when appropriate, suggest that the patient seek professional advice, as depression may exacerbate the effects of AMD.[282]

SOCIOECONOMIC CONSIDERATIONS

Direct medical costs (taken from private insurance and Medicare claims data) related to treatment for AMD in the United States were estimated to be approximately $574 million in 2004.[283] However, these studies were conducted prior to the use of anti-VEGF agents.

The considerable burden of disease associated with AMD, as well as the public health benefits of prevention, are highlighted in analyses conducted by the AREDS authors. This research, published in 2003, estimated that 8 million Americans aged 55 and older are at high risk for developing advanced AMD. If these persons received AREDS-formulation supplements, it was estimated that approximately 300,000 would avoid advanced AMD and any associated vision loss over a 5-year period.[284] In the Salisbury Eye Study, Christ et al reported that VA loss adversely affected activities of

daily living levels which subsequently increased mortality risk in older adults, further calculations estimated that treating AMD with anti-VEGF agents saves 1 to 2 years of life.[285]

More recent cost-effectiveness studies on the use of anti-VEGF therapies have demonstrated this newer therapy to be highly cost-effective over prior therapies such as PDT.[286 287-290] The off-label use of intravitreal bevacizumab was suggested to represent a highly cost-effective, off-label option for management of neovascular AMD compared with the higher cost of ranibizumab.[289] Others have investigated the cost utility of various treatments for AMD. One analysis using CATT trial data found that bevacizumab with PRN dosing offered considerably greater value than ranibizumab in the treatment of neovascular AMD among patients 80 and older.[290] Another analysis using CATT and MARINA data evaluated the relative 10-year cost-effectiveness of bevacizumab and ranibizumab in 65-year-old patients with neovascular AMD. This study estimated the cost utility of bevacizumab treatment (relative to no treatment) at approximately $2,700 per quality-adjusted life year ([QALY] for monthly dosing) and $3,300 per QALY (for PRN dosing). In contrast, the cost-effectiveness of ranibizumab was estimated as $63,300/QALY for monthly dosing and $18,600 per QALY for PRN dosing.[287] Wholesale prices of anti-VEGF medications range from $50 to $1,950 per dose, depending on the medication.[291,292] The use of personalized anti-VEGF treatment guided by OCT has resulted in savings for the US government in neovascular AMD patients of $9 billion and $22 billion, respectively.[293]

APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual, and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced, and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility.

They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn they respond in an adequate and timely manner. The ophthalmologist maintains complete and accurate medical records.

- On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- The ophthalmologist and those who assist in providing care identify themselves and their profession.
- For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.

- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices, or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES [All]

Age-related macular degeneration, which includes entities with the following ICD-9 and ICD-10 classifications (see Glossary):

ICD-9 CM	ICD-10 CM
Macular degeneration, dry – 362.51	Nonexudative AMD – H35.31
Macular degeneration, wet – 362.52	Exudative AMD – H35.32
Macular drusen – 362.57	Drusen (degenerative) of macula – H35.36-

ICD = International Classification of Diseases; CM = Clinical Modification used in the United States

- AMD = age-related macular degeneration; does not require laterality indicators
- Macular drusen; (–) = 1, right eye; 2, left eye; 3, bilateral

Additional information for ICD-10 codes:

- Certain ICD-10 CM categories have applicable 7th characters. The applicable 7th character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7th character must always be the 7th character in the data field. If a code that requires a 7th character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

GLOSSARY

Advanced age-related macular degeneration (advanced AMD): This is the most severe form of AMD, defined as geographic atrophy involving the center of the macula (fovea) or features of CNV.

Age-Related Eye Disease Study (AREDS): A prospective, multicenter, randomized clinical trial designed to assess the natural course and risk factors of age-related cataract and AMD and the effects of antioxidants and minerals on these two conditions.

Age-Related Eye Disease Study (AREDS2): A prospective, multicenter, randomized clinical trial of 4000 participants designed to assess the effects of oral supplementation of high doses of macular xanthophylls (lutein and zeaxanthin) and/or omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid) for the treatment of AMD and cataract. All participants were offered the AREDS supplements. A secondary randomization evaluated the possibility of deleting beta-carotene and decreasing the original levels of zinc in the AREDS formulation. Follow-up occurs over 5 years.

Age-related macular degeneration (AMD): There is no universally accepted definition of this term. The condition is characterized by the presence of drusen and alterations of the RPE as well as by the fundus abnormalities associated with CNV, and it generally occurs in persons over age 65. The VA may vary from normal to severe impairment.

AMD: See Age-related macular degeneration.

Amsler grid: This is a graph paper with a central dot for fixation. While viewing this central spot, the patient is asked to evaluate vision for the early signs of metamorphopsia by looking for any changes in the grid.

ANCHOR Study: Anti-VEGF antibody (ranibizumab) for the treatment of predominantly classic CNV in AMD study.

Anti-VEGF: See Anti-vascular endothelial growth factor.

Anti-vascular endothelial growth factor (VEGF): Substances that inhibit the action of vascular endothelial growth factor protein.

AREDS: See Age-Related Eye Disease Study (AREDS).

AREDS2: See Age-Related Eye Disease Study (AREDS2).

Bevacizumab (Avastin): Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF and has FDA approval for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer.

CATT: See Comparison of AMD Treatment Trials.

Choroidal neovascularization (CNV): Synonymous with subretinal or choroidal neovascular membrane. These are vessels from the choriocapillaris that perforate and grow through Bruch's membrane and enter the subretinal pigment epithelial and/or subretinal spaces.

Classic choroidal neovascularization: The angiographic findings in which the CNV is recognized in the early phase of the fluorescein angiogram as an area of bright, well-demarcated hyperfluorescence and during the late phases of the angiogram as progressive pooling of dye in the overlying subsensory retinal space. Usually considered a Gass Type 2 membrane.

CNV: See Choroidal neovascularization.

Comparison of AMD Treatment Trials (CATT): A multicenter clinical trial that compared the safety and efficacy of bevacizumab and ranibizumab and an individualized dosing regimen (PRN) to monthly injections.

DENALI study: Part of the SUMMIT studies, this trial compares ranibizumab and verteporfin PDT combination therapy with ranibizumab alone.

Disc area: As defined by the Macular Photocoagulation Study, the area of a circle with a diameter of 1.5 millimeters (1500 μm) equal to 1.77 square millimeters. The area on a photograph will vary with the type of fundus camera used.

Disciform scar: Subretinal fibrovascular tissue that usually becomes more fibrous within a few years and that is often the end result of CNV.

Drusen: Yellow lesions at the level of the basement membrane of the RPE. They are the ophthalmoscopic and histologic hallmark of AMD. They are considered to be small if they are less than 63 μm in diameter, intermediate if they are greater than or equal to 63 and less than or equal to 125 μm, and large when the diameter is greater than 125 μm, and they may be considered soft if they have ill-defined edges.

EVEREST study: A study conducted in Asia that investigated combination PDT and anti-VEGF therapy.

Extrafoveal choroidal neovascularization: A choroidal neovascular membrane that comes no closer than 200 μm from the center of the foveal avascular zone, as defined by the Macular Photocoagulation Study.

Foveal avascular zone: An area usually 300 to 500 millimeters in diameter centered on the foveola and lacking retinal blood vessels, also known as the capillary-free zone.

Geographic atrophy: One or several well-demarcated zones of RPE atrophy (and sometimes choriocapillaris atrophy). Drusen are usually present surrounding these zones and there may be surrounding pigment clumping. This is an advanced form of AMD when the center of the fovea is involved.

HARBOR study: A 12-month dose-comparison study of 0.5 mg and 2 mg of ranibizumab. It also compared monthly to PRN treatment over 2 years.

ICD-9: International Statistical Classification of Diseases and Related Health Problems, Ninth Edition.

ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Edition.

ICG: See Indocyanine green.

Indocyanine green (ICG): A cyanine dye that fluoresces in the near-infrared spectrum and is used in diagnostic evaluation to visualize CNV.

Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN trial): This study compared intravitreal bevacizumab with ranibizumab dosed either on a continuous (monthly) or discontinuous (PRN) basis. It was a 2-year study conducted in the United Kingdom.

IVAN trial: See Inhibition of VEGF in Age-related choroidal Neovascularization.

Juxtafoveal choroidal neovascularization: Well-demarcated CNV that is between 1 μm and 199 μm from the center of the foveal avascular zone but that does not reach its center, as defined by the Macular Photocoagulation Study.

LUCAS: Lucentis Compared to Avastin Study

Macular Photocoagulation Study (MPS): A series of prospective randomized multicenter clinical trials designed to determine the efficacy of laser photocoagulation surgery in CNV caused by AMD, ocular histoplasmosis, and idiopathic causes.

Macular translocation: An operation designed to move the sensory retina from an area of damaged RPE to another area of more intact RPE.

MARINA study: Study of minimally classic/occult trial of the anti-VEGF antibody, ranibizumab, in the treatment of neovascular AMD.

MONT BLANC study: Part of the SUMMIT study, this European trial compares ranibizumab and verteporfin PDT combination treatment with ranibizumab alone.

MPS: See Macular Photocoagulation Study.

Neovascular macular degeneration: Manifestations of CNV and/or RPE detachment associated with subretinal serous fluid, exudates, and/or blood.

Occult choroidal neovascularization: Angiographic findings characterized by a fibrovascular RPE detachment and/or late leakage of an undetermined source. This is also referred to as poorly defined CNV that has indistinct or poorly demarcated boundaries on fluorescein angiography. Usually considered a Gass Type 1 membrane.

Optical coherence tomography (OCT): A noninvasive technique to image intraocular tissues by measuring the echo time delay and intensity of back-reflected light. The resulting image provides high-resolution, cross-sectional representation of structure with near-histological detail.

Optical coherence tomography angiography (OCTA): A non-invasive imaging technique for the microvasculature of the retina and choroid.

PDT: See Photodynamic therapy.

PED: See Pigment epithelial detachment.

Pegaptanib sodium (Macugen): A compound that binds to a specific isoform of vascular endothelial growth factor ($VEGF_{165}$) and thus blocks its activity. It is administered by intravitreal injection.

Persistent choroidal neovascularization: Angiographically documented CNV found within 6 weeks of laser surgery, typically but not always at the site of the previously treated CNV, according to the Macular Photocoagulation Study definition.

Photodynamic therapy (PDT): A method of treating CNV with a two-part process involving systemic administration of a photosensitizing drug followed by nonthermal light application to the macular pathology.

Pigment epithelial detachment (PED): Accumulation of fluid (serous RPE detachment) or blood (hemorrhagic RPE detachment) beneath the RPE. Associated CNV is usually present in older patients and/or patients with drusen. Another form is the fibrovascular pigment epithelial detachment, which is a form of occult CNV.

PGF: See Placental growth factor.

Placental growth factor (PGF): A growth factor related to VEGF that may play a role in ocular angiogenesis.

Polypoidal choroidopathy: Characterized by multiple and recurrent serosanguineous RPE detachments, which often resemble hemorrhagic detachment in AMD. A fluorescein angiogram and ICG may be helpful in distinguishing these conditions.

Predominantly classic lesion: CNV in which classic CNV occupies more than 50% of the entire lesion area.

Ranibizumab (Lucentis): A recombinant humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment that binds to and inhibits the biologic activity of a form of VEGF-A.

Recurrent choroidal neovascularization: Angiographically documented CNV found more than 6 weeks after laser surgery and typically occurring on the perimeter of the previous treatment scar, as defined by the Macular Photocoagulation Study.

Reticular pseudodrusen: Also referred to as subretinal drusenoid deposits.

Retinal angiomatous proliferation: Characterized by proliferation of retinal capillaries in the paramacular area that may present as intraretinal, subretinal, or CNV.

Retinal pigment epithelial (RPE) abnormalities: Alterations of the retinal pigment epithelium-Bruch's membrane complex that lead to an appearance of hypopigmentation and/or hyperpigmentation. Its extreme form is geographic atrophy.

RPE: See Retinal pigment epithelium (RPE) abnormalities.

Severe visual loss: In this document, severe visual loss means quadrupling or more of the visual angle (e.g., 20/20 to 20/80 or worse, or 20/50 to 20/200 or worse).

Subfoveal choroidal neovascularization: CNV that underlies the center of the foveal avascular zone.

SST: See Submacular Surgery Trial.

Submacular Surgery Trial (SST): A trial conducted in the mid-1990s, prior to the emergence of currently used therapies, that evaluated the efficacy of submacular surgery for treating complications of CNV and subretinal hemorrhage.

Subretinal drusenoid deposits: See Reticular pseudodrusen.

SUMMIT: Two studies, called DENALI in North America and MONT BLANC in Europe, that compare ranibizumab and verteporfin PDT combination therapy with ranibizumab alone.

Vascular endothelial growth factor (VEGF): A significant mediator in the process of angiogenesis and increased vascular permeability and inflammation. It has been identified in neovascularization related to both diabetic retinopathy and AMD. In animal models, the introduction of VEGF has initiated the cascade of neovascularization seen in AMD. Thus, the inhibition or antagonism of the action of VEGF is a targeted area of research, with several novel therapeutic agents being developed, and in various stages of investigation and FDA approval.

VEGF: See Vascular endothelial growth factor.

Verteporfin (Visudyne): A drug used as a photosensitizer in conjunction with a nonthermal PDT laser.

VIEW Study: VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD

LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed and Cochrane databases were conducted in March 2018; the search strategies are provided at www.aao.org/ppp. Specific limited update searches were conducted after June 2019.

"Macular Degeneration/diagnosis"[Mesh]

("Macular Degeneration/epidemiology"[Mesh] OR "Macular Degeneration/ethnology"[Mesh])

"Macular Degeneration/genetics"[Mesh]

"Macular Degeneration"[Mesh] AND "Risk Factors"[Mesh]

("Macular Degeneration/therapy"[Mesh] AND "Quality of Life"[Mesh]) OR ("Macular Degeneration"[Mesh]) AND ("Quality of Life"[Mesh] not treatment) OR ("Macular Degeneration"[Mesh] AND "Cost of Illness"[Mesh])

("Macular Degeneration/economics"[Mesh] OR ("Macular Degeneration"[Mesh] AND "Cost-Benefit Analysis"[Mesh])) NOT "Cost of Illness"[Mesh]

("Macular Degeneration/therapy"[Mesh] OR ("Macular Degeneration"[Mesh] AND (combinations[tiab] OR combined[tiab])) OR (("Drug Therapy, Combination"[Mesh] OR "Drug Combinations"[Mesh]) OR "Combined Modality Therapy"[Mesh])

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course
Retina and Vitreous (Section 12, 2019–2020)

Focal Points
Neovascular Age-Related Macular Degeneration (2016)
Masquerades of Age-related Macular Degeneration (2018)

Ophthalmic Technology Assessment –
Published in *Ophthalmology*, which is distributed free to Academy members; links to full text available at www.aao.org/ota.
Safety and Efficacy of Anti-Vascular Endothelial Growth Factor Therapies for Neovascular Age-Related Macular Degeneration (2018)

Patient Education
Age-Related Macular Degeneration Brochure (AMD) (2014)
AMD and Nutritional Supplements Brochure (2014)
Anti-VEGF Treatment for AMD Brochure (2014)

Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp.
Comprehensive Adult Medical Eye Evaluation (2015)

To order any of these products, except for the free materials, please contact the Academy's Customer Service at 866.561.8558 (U.S. only) or 415.561.8540 or www.aao.org/store

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