Age-Related Macular Degeneration
As a service to its members and the public, the American Academy of Ophthalmology has developed a series of guidelines called Preferred Practice Patterns that identify characteristics and components of quality eye care. (See Appendix 1.)

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.

Preferred Practice Patterns 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 meet the needs of all patients. Adherence to these Preferred Practice Patterns 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.

The 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.

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Innovation in medicine is essential to assure 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 PPPs 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 developed by the Academy’s H. Dunbar Hoskins Jr., M.D. Center for Quality Eye Care without any external financial 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 before publication.
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INTRODUCTION

The Preferred Practice Pattern® (PPP) guidelines have been written on the basis of three principles.

- Each Preferred Practice Pattern should be clinically relevant and specific enough to provide useful information to practitioners.
- Each recommendation that is made should be given an explicit rating that shows its importance to the care process.
- Each recommendation should also be given an explicit rating that shows the strength of evidence that supports the recommendation and reflects the best evidence available.

In the process of revising this document, a detailed literature search of articles in the English language was conducted on the subject of age-related macular degeneration for the years 2002 to 2007. The results were reviewed by the Retina Panel and used to prepare the recommendations, which they rated in two ways.

The panel first rated each recommendation according to its importance to the care process. This “importance to the care process” rating represents care that the panel thought would improve the quality of the patient’s care in a meaningful way. The ratings of importance are divided into three levels.

- Level A, defined as most important
- Level B, defined as moderately important
- Level C, defined as relevant but not critical

The panel also rated each recommendation on the strength of evidence in the available literature to support the recommendation made. The “ratings of strength of evidence” also are divided into three levels.

- Level I includes evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial. It could include meta-analyses of randomized controlled trials.
- Level II includes evidence obtained from the following:
  - Well-designed controlled trials without randomization
  - Well-designed cohort or case-control analytic studies, preferably from more than one center
  - Multiple-time series with or without the intervention
- Level III includes evidence obtained from one of the following:
  - Descriptive studies
  - Case reports
  - Reports of expert committees/organizations (e.g., PPP panel consensus with external peer review)

The evidence cited is that which supports the value of the recommendation as something that should be performed to improve the quality of care. The panel believes that it is important to make available the strength of the evidence underlying the recommendation. In this way, readers can appreciate the degree of importance the committee attached to each recommendation and they can understand what type of evidence supports the recommendation.

The ratings of importance and the ratings of strength of evidence are given in bracketed superscripts after each recommendation. For instance, “[A:II]” indicates a recommendation with high importance to clinical care [A], supported by sufficiently rigorous published evidence, though not by a randomized controlled trial [II].

The sections entitled Orientation and Background do not include recommendations; rather they are designed to educate and provide summary background information and rationale for the recommendations that are presented in the Care Process section. A summary of the major recommendations for care is included in Appendix 2.
ORIENTATION

ENTITY
Age-related macular degeneration (ICD-9 #362.50, 362.51, and 362.52).

DISEASE DEFINITION
Age-related macular degeneration (AMD) is a disorder of the macula and is characterized by one or more of the following:
- Drusen formation
- Retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- Geographic atrophy of the RPE and choriocapillaris
- Neovascular (exudative) maculopathy

There are a number of classifications of AMD in the literature. This PPP will use the classification of the Age-Related Eye Disease Study (AREDS) to define the early and intermediate stages of AMD, because the current treatment recommendations are based on this classification. The AREDS was a prospective multicenter randomized clinical trial conducted between 1992 and 2006 designed to assess the natural course and risk factors of age-related cataract and AMD and the effects of antioxidant vitamins and minerals on these two ocular conditions.

The classification of AMD from the AREDS is as follows:1

No AMD (AREDS category 1) was the control group for the AREDS and had no or few small drusen (<63 microns in diameter).

Early AMD (AREDS category 2) consists of a combination of multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or RPE abnormalities.

Intermediate AMD (AREDS category 3) consists of extensive intermediate drusen, at least one large druse (≥125 microns in diameter), or geographic atrophy 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 and choriocapillaris involving the center of the fovea
- Neovascular maculopathy such as the following:
  - Choroidal neovascularization (CNV)
  - Serous and/or hemorrhagic detachment of the sensory retina or RPE
  - Retinal hard exudates (a secondary phenomenon resulting from chronic leakage from any source)
  - Subretinal and sub-RPE fibrovascular proliferation
  - Disciform scar

See Glossary for definitions of important terms. Clinical details are available in standard texts.2,3

PATIENT POPULATION
Patients are typically aged 50 years or older, with or without visual symptoms.

ACTIVITY
Evaluation and management of patients with AMD.

PURPOSE
The primary purpose of evaluation and management is to minimize or reverse loss of vision and to maximize the vision-related quality of life related to AMD.
GOALS

- 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, treatment, and follow-up examinations.
- Help patients identify sources for visual rehabilitation.

BACKGROUND

EPIDEMIOLOGY

Age-related macular degeneration is a leading cause of severe, irreversible vision impairment in developed countries.\(^4\) Approximately 1.75 million people age 40 years or older in the United States have neovascular AMD or geographic atrophy and 7.3 million have large drusen (≥125 microns) in one or both eyes. In the United States, AMD causes approximately 46% of cases of severe visual loss (visual acuity 20/200 or worse) in persons older than 40.\(^9\) Although an estimated 80% of AMD patients have the non-neovascular form,\(^2\) the neovascular form is responsible for almost 90% of the severe visual loss (visual acuity 20/200 or worse) due to AMD.\(^10\) The prevalence, incidence, and progression of AMD and most associated features (e.g., large drusen) increase with age. In the Beaver Dam Eye Study, in which the study population consists mostly of white men and women, prevalence of any AMD (referred to as age-related maculopathy) was less than 10% in persons aged 43 to 54 years but more than tripled for persons aged 75 to 85 years.\(^4\) The Beaver Dam Eye Study demonstrated that progression to any AMD in a 10-year period was 4.2% for persons aged 43 to 54 years and 46.2% for those aged 75 years and older.\(^11\) The Beaver Dam Eye Study has identified soft, indistinct drusen and pigmentary abnormalities, which also increase in frequency with increasing age, as strongly predictive of advanced AMD. In the Los Angeles Latino Eye Study, prevalence of advanced AMD increased from 0% in individuals 40 to 49 years of age to 8.5% in those 80 years old and older.\(^12\) 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 age 50 to 59 years to 4.3% in those aged 80 and older.\(^13\) Prevalence of AMD varies by ethnicity.\(^9,14-16\) Observations from the Barbados Eye Study,\(^17\) the Baltimore Eye Study,\(^18\) and the Macular Photocoagulation Study (MPS)\(^19\) suggest that late stages of AMD are more common among whites than blacks. Findings from the Multi-ethnic Study of Atherosclerosis also suggest that neovascular AMD may be more common in whites than blacks. A surprising finding of this study that needs to be confirmed in other studies is that neovascular AMD may be even more common among Chinese Americans than Hispanic, black, or white Americans.\(^15\)

Direct medical costs (taken from private insurance and Medicare claims data) related to treatment for AMD were estimated at $574 million for 2004.\(^20\) In another study, Medicare direct medical costs from 1995 to 1999 (before the introduction of photodynamic therapy [PDT] and antiangiogenic pharmacotherapy) were estimated at $569 million annually out of the $6 billion estimated total cost of eye care services for Medicare in 1999.\(^21\) The aging population and antiangiogenic pharmacotherapy are anticipated to cause an increase in these costs.

RISK FACTORS

The main risk factor for the development of advanced AMD is increasing age. Although a number of risk factors have been investigated, cigarette smoking is the only risk factor other than age and ethnicity that has been consistently identified in numerous studies.\(^22-29\) Smoking doubles the risk of AMD, and there appears to be a dose response whereby increasing odds are associated with an increased number of pack-years smoked.\(^24\) Smoking cessation was associated with a reduced risk for AMD; the risk of developing AMD in those who had not smoked for over 20 years was comparable to the risk in nonsmokers.\(^24\) Other factors that may play a role in AMD are...
hypothesis and other underlying atherosclerotic disease processes. A number of case-control and population-based studies that examined the relationship between AMD and hypertension or other cardiovascular disease show conflicting findings. Additional risk factors may include low 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, lutein/zeaxanthin, and zinc as risk factors for AMD. The AREDS results show a beneficial effect of high doses of 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%. Several studies have also identified an association between dietary fat and advanced AMD. Similar to the reports on risk factors for cardiovascular disease, a number of reports from population-based studies have demonstrated a decreased risk of AMD associated with higher dietary intake of omega-3 long-chain polyunsaturated fatty acids, commonly found in fish. Increased risk of AMD was found in individuals with a higher intake of saturated fats and cholesterol, and in those with a higher body mass index. Markers of inflammation, such as C-reactive protein, may be associated with a higher risk of AMD progression. It is important to recognize that any associations found in these observational studies of risk factors cannot be interpreted as factors that have a definite causal relationship. Such associations may not necessarily translate into treatment recommendations.

Other factors that have been considered in various studies, with inconclusive findings, include hormonal status, sunlight exposure, and alcohol use.

The role of heredity has been supported by epidemiologic studies of families with affected members and by twin studies. Recent studies have identified complement factor H (CFH) and LOC387715/HtrA1 genes as major risk factors for AMD. The complement factor H gene regulates the complement system, which regulates the immune system’s attack on infection and abnormal cells while sparing normal cells. Complement factor H is an inhibitory gene of the complement system of innate immunity. Other genetic associations with AMD in the complement pathway include complement factor B, complement component 2, and complement component 3. Patients homozygous for the Y402H risk allele of CFH possess a 7.4-fold increased risk of AMD. The complement factor H gene is found on chromosome 1, in a region linked to AMD in multiple family studies. Studies have reported an association of a complement factor H variant (homozygous individuals) with other factors in the risk of progression to advanced AMD compared with noncarriers lacking these determinants. These factors include elevated erythrocyte sedimentation rates (20-fold increase), elevated serum C-reactive protein (27-fold increase), and smoking (34-fold increase). The findings suggest that, in addition to the interplay of environmental factors and heredity, inflammation may play a role in the pathogenesis of AMD.

**NATURAL HISTORY**

**Early AMD**

As defined by the AREDS, early AMD (category 2) is characterized by small and intermediate drusen and minimal or no pigment epithelial abnormalities in the macula. Patients in this category generally have a central visual acuity similar to those of patients who have normal maculae. In the AREDS, patients with early (or low-risk) AMD had a 1.3% risk of progressing to advanced AMD at 5 years in either eye.

**Intermediate AMD**

Intermediate AMD (category 3) has been defined by the AREDS as having extensive medium-sized drusen or one or more large drusen (≥125 microns in diameter) in one or both eyes. The progression to advanced AMD at 5 years in this group is approximately 18% in the AREDS. However, for patients with large drusen in one eye, the rate of development of advanced AMD at 5 years is 6.3%, while the rate for patients with bilateral large drusen is 26% at 5 years.
Advanced AMD

Advanced AMD (category 4) as defined in the AREDS refers to either neovascular AMD or geographic atrophy involving the center of the macula (fovea). Visual acuity is generally already affected in 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 in the remaining good eye.77

Geographic atrophy, the advanced form of non-neovascular AMD, may consist of one or more zones of well-demarcated RPE and/or choriocapillaris atrophy. Drusen and other pigmentary abnormalities may surround the atrophic areas. Severe visual loss occurs less commonly in patients with geographic atrophy than in patients with neovascular AMD, nevertheless, geographic atrophy involving the center of the fovea causes approximately 10% of all AMD-related visual loss of 20/200 or worse.78 Patients with geographic atrophy often have relatively good distance visual acuity but a substantially decreased capacity for near visual tasks such as reading.79 Doubling of the visual angle has been reported to occur in as many as 50% of patients over a 2-year period.78 Choroidal neovascularization also can occur.

Neovascular AMD is characterized clinically and angiographically by occult, classic, or mixed occult-classic CNV; serous and/or hemorrhagic detachment of the sensory retina or RPE; and/or various stages of an elevated, fibrovascular disciform scar.

In the MPS, the classification of neovascular AMD with CNV was based on fluorescein angiography. Classic CNV is a well-demarcated hyperfluorescence in the early phase of the angiogram, with progressive pooling of dye in the overlying subsensory retinal space during the late phases of the angiogram. Occult neovascularization is characterized by fibrovascular pigment epithelial detachment (PED), an irregular elevation of the RPE with stippled or granular irregular fluorescence first seen early in the angiogram, with progressive leakage in the later phase of the angiogram.

Other clinical subtypes of neovascular AMD include the following:

- Serous retinal PED (with or without neovascularization)80
- Polypoidal choroidopathy80
- Retinal angiomatous proliferation81

The AREDS described a simplified clinical scale defining risk categories for development of advanced AMD.82 The grading system assigns to each eye one risk factor for the presence of one or more large drusen (>125 microns, width of a large vein at disc margin) and one risk factor for the presence of any pigment abnormality. Risk factors are summed across both eyes, yielding a 5-step scale (0-4) on which the approximate 5-year risk of developing advanced AMD in at least one eye increases in this easily remembered sequence: zero factors, 0.5%; one factor, 3%; two factors, 12%; three factors, 25%; and four factors, 50%. For persons with no large drusen, the presence of intermediate drusen in both eyes is counted as one risk factor. Advanced AMD in one eye is counted as two risk factors. Often such eyes also have large drusen and RPE hypo/hyperpigmentary changes; they are considered to have four risk factors, the highest risk-level of all patients with AMD.

RATIONALE AND MODALITIES FOR TREATMENT

The cause of AMD is believed to be multifactorial. Prospective randomized controlled clinical trials support the use of antioxidant vitamins and mineral supplements, intravitreal injection of antivascular endothelial growth factor (VEGF) agents, PDT, and laser photocoagulation surgery to treat AMD.

Early AMD

The AREDS used a factorial design in which 4,757 participants were randomized to antioxidant vitamins, zinc, a combination of antioxidant vitamins and zinc, or a placebo, and they were followed for a mean of 6 years.1 Of these, 3,640 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 (see Table 1). In early AMD (AREDS category 2), only 1.3% of participants progressed to advanced AMD in 5 years. 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. Approximately two-thirds of the study participants took an additional multivitamin (Centrum, Wyeth Consumer Healthcare, Madison, NJ) that had no effect on the clinical outcome.

### Intermediate AMD

In the AREDS, the participants who benefited from antioxidant vitamin and mineral supplementation were those with either intermediate AMD or advanced AMD in one eye. For participants with extensive 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% by the combination treatment of all the antioxidant vitamins with zinc and copper. The risk of losing vision of three or more lines (doubling of the visual angle) also was reduced by 19% by 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 (see Table 2).

### Table 1: Antioxidant Vitamin and Mineral Supplements Used in the Age-Related Eye Disease Study

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Daily Dose*</th>
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<tr>
<td>Vitamin C</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>15 mg (25,000 IU)</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>80 mg</td>
</tr>
<tr>
<td>Cupric oxide</td>
<td>2 mg</td>
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* 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.


### Table 2: Summary of Results of AREDS for Developing Advanced AMD and Vision Loss

<table>
<thead>
<tr>
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<th>Antioxidants Plus Zinc</th>
<th>Zinc Alone</th>
<th>Antioxidants Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of the relative risk of developing advanced AMD</td>
<td>25%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Reduction of the relative risk of vision loss (three or more lines)</td>
<td>19%</td>
<td>11%</td>
<td>10%</td>
</tr>
</tbody>
</table>

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

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.

Other investigators raised concerns about the methodology for this meta-analysis; their concerns included a potential bias in the analyses due to the deletion of clinical trials that had no deaths and the lack of biological plausibility in their interpretation of the results of the subgroup analyses.

A number of studies in the meta-analysis used antioxidant dosages much higher than those used in the AREDS, which did not find an adverse association of high-dose antioxidant supplementation. Two studies reported an increased incidence of mortality among patients who were heavy smokers and were taking beta-carotene supplements to prevent lung cancer.

The decision to take the AREDS supplement formulation must balance possible risks with possible benefit. Current smokers and patients with a smoking history should be advised to avoid taking beta-carotene and consider taking the other components of the AREDS formulation.

### Neovascular AMD

With the introduction of the VEGF inhibitors pegaptanib sodium (Macugen, Eyetech, Inc., Cedar Knolls, NJ) in December 2004 and ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) in June 2006, effective treatments for neovascular AMD now exist. The VEGF inhibitors demonstrated improved visual outcomes compared with other therapies and have become the first-line therapy for treating neovascular AMD.

Ranibizumab intravitreal injection has Food and Drug Administration (FDA) approval for the treatment of all subtypes of neovascular AMD based on results from three double-masked randomized controlled trials (see Table 3 and Appendix 3). Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment developed for intraocular use that binds to and inhibits the biologic activity of all isoforms of human VEGF-A.

Bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) is a full-length monoclonal antibody that binds all isoforms of VEGF. It has FDA approval 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 before FDA approval of ranibizumab. Because preliminary reports appeared favorable, ophthalmologists began to use intravitreal bevacizumab off-label to treat choroidal neovascularization. There are no long-term results on the safety and effectiveness of the use of intravitreal bevacizumab for neovascular AMD. There are short-term uncontrolled case series that report improvements in visual acuity and decreased retinal thickness by optical coherence tomography. Informed consent information is available on the benefits and risks of intravitreal bevacizumab and its off-label status.

Because ranibizumab and bevacizumab have not been evaluated directly in a randomized controlled trial, the Comparison of AMD Treatment Trials (CATT), a multicenter clinical trial to compare the relative safety and effectiveness of ranibizumab and bevacizumab, is under way. The CATT will also investigate whether a reduced dosing schedule (monthly as needed) is as effective as a fixed schedule of monthly injections because the optimal dosing strategy for the anti-VEGF agents has not yet been determined. Further investigation beyond this study may be needed to evaluate other types of schedules for delivering anti-VEGF therapy. Determining the relative safety, efficacy, and dosing schedule is important, because wholesale prices of the medications range from $1,950 per dose for ranibizumab, $995 per dose for pegaptanib, to less than $50 per dose for bevacizumab.

Pegaptanib sodium is a selective VEGF antagonist that binds only to the 165 isoform of VEGF-A. Pegaptanib sodium injection has FDA approval for the treatment of all subtypes of neovascular AMD, with a recommended dosage of 0.3 mg injected every 6 weeks into the vitreous based on results from two double-masked randomized controlled trials (see Table 3 and Appendix 3).

Randomized trials are under way to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various combinations with verteporfin PDT, following the publication of results from uncontrolled case series. Current published reports of this off-label use of
intravitreal injection of corticosteroids do not provide conclusive evidence of benefit, and there are limited data on risk.

Ongoing trials of combination treatment for AMD include the DENALI and MONT BLANC studies (ranibizumab and verteporfin PDT compared with ranibizumab alone), the Verteporfin Intravitreal Triamcinolone Acetonide Study (VERITAS), the Visudyne with Intravitreal Triamcinolone Acetonide (VisTA) study, and the Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD (LEVEL), which compares anti-VEGF therapy plus pegaptanib sodium.

Subfoveal CNV
In addition to intravitreal injections of VEGF inhibitors, verteporfin PDT and thermal laser photocoagulation surgery are FDA-approved options for the treatment of subfoveal lesions. Photodynamic therapy with verteporfin has FDA approval for the treatment of predominantly classic neovascular AMD; treatment trial results are described in Appendix 3. The efficacy of thermal laser photocoagulation surgery for CNV was studied in the MPS, a randomized controlled multicenter study. In the MPS, 22% of eyes treated for subfoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 47% of untreated eyes after 4 years of follow-up. Because of the loss of vision associated with laser photocoagulation surgery (82% of treated patients have a resultant in visual acuity worse than 20/200), photocoagulation is no longer in general clinical use for subfoveal neovascularization.

Table 3 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 CNV
Although randomized controlled clinical trials did not include 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. Most of these lesions will recur regardless of treatment, and it is assumed that many will be eligible for retreatment as recurrent subfoveal CNV lesions with intravitreal injection of an anti-VEGF agent (off-label use) or PDT with verteporfin.

Photocoagulation of well-demarcated juxtafoveal CNV lesions resulted in a small overall treatment benefit. 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. Persistent or recurrent leakage after treatment was associated with a greater incidence of severe visual loss. 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.

Extrafoveal CNV
There is still a role for thermal laser treatment in eyes with extrafoveal CNV lesions as defined by the MPS. Photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a substantial reduction in the risk of severe visual loss for the first 2 years. A recurrence rate of approximately 50% reduced this benefit over the subsequent 3 years of follow-up. After 5 years of follow-up, 48% of eyes treated for extrafoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 62% of untreated eyes.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Patient Characteristics</th>
<th>Duration and Frequency of Treatment</th>
<th>Treated Eyes</th>
<th>Untreated Eyes</th>
<th>Years after Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCHOR (ranibizumab injection)</td>
<td>423</td>
<td>Mean age 77 years; BCVA 20/40 to 20/320; total lesion size ≤5400 mm; no previous treatment (including verteporfin therapy) that might compromise an assessment of the study treatment</td>
<td>Monthly injections for 1 year Verteporfin or sham on day 0 and then as needed following FA at months 3, 6, 9, or 12</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 4% (treated only with ranibizumab 0.5 mg)</td>
<td>Visual Gain of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 40% (treated only with ranibizumab 0.5 mg)</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; n/a (all patients received treatment)</td>
</tr>
<tr>
<td>MARINA (ranibizumab injection)</td>
<td>716</td>
<td>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</td>
<td>Monthly injections for 2 years</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 8% (0.3 mg)</td>
<td>Visual Gain of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 26% (0.3 mg)</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 47%</td>
</tr>
<tr>
<td>PIER (ranibizumab injection)</td>
<td>184</td>
<td>Mean age 78 years; BCVA 20/40 to 20/320; primary or recurrent subfoveal CNV, with the total CNV area (classical plus occult CNV) ≥50% of total lesion size; minimally classic or occult with no classic CNV only if criteria met for presumed disease progression. Any prior treatment with verteporfin PDT or antiangiogenic agent excluded</td>
<td>Injections every month for 3 doses, then doses every 3 months</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 17% (0.3 mg)</td>
<td>Visual Gain of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 12% (0.3 mg)</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 51%</td>
</tr>
<tr>
<td>TAP (verteporfin PDT)</td>
<td>609</td>
<td>Mean age 75 years; BCVA 20/40 to 20/200; classic CNV or occult CNV if &gt;50% of total lesion size</td>
<td>Following first treatment, retreatment was considered every 3 months per FA findings through 21 months of follow-up</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 47%</td>
<td>Visual Gain of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 8%</td>
<td>Visual Loss of 15 Letters or More&lt;sup&gt;a&lt;/sup&gt; 62%</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Patient Characteristics</td>
<td>Duration and Frequency of Treatment</td>
<td>Treated Eyes</td>
<td>Untreated Eyes</td>
<td>Years after Enrollment</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>VIP (verteporfin PDT)</td>
<td>339</td>
<td>Mean age 75 years; subfoveal CNV lesions ≤5400 μm with either occult with no classic CNV, BCVA at least 20/100, evidence of hemorrhage or progression; or classic CNV with BCVA at least 20/40</td>
<td>Following first treatment, retreatment was considered every 3 months per FA findings through 24 months of follow-up</td>
<td>54%</td>
<td>5%</td>
<td>67% 1% 2</td>
</tr>
<tr>
<td>VISION (pegaptanib sodium injection)†</td>
<td>590</td>
<td>Age ≥50 years; BCVA 20/40 to 20/320; subfoveal CNV with total lesion size ≤12 disc areas; IOP ≤23 mmHg</td>
<td>Injection every 6 weeks for 54 weeks (9 total treatments); then re-randomized and injection every 6 weeks through week 96 (8 total treatments)</td>
<td>45%</td>
<td>10%</td>
<td>59% 4% 2</td>
</tr>
</tbody>
</table>

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; FA = fluorescein angiography; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; PDT = photodynamic therapy; PIER = A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Neovascularization with or without Classic CNV; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy; VISION = VEGF Inhibition Study in Occular Neovascularization

* Defined as doubling of the visual angle.
† Predominantly classic.
‡ Pegaptanib sodium injection was administered to patients who were allowed both prior and on-study PDT.
PREVENTION AND EARLY DETECTION

Patients with early AMD and/or a family history of AMD should be encouraged to have regular dilated eye exams for the early detection of the intermediate stage of AMD. Treatment with antioxidants and minerals as described in the AREDS is recommended for patients who have progressed to intermediate or advanced AMD in one eye.

Patients with intermediate AMD who are at increased risk of visual loss or of progression to advanced AMD should be educated about methods of detecting new symptoms of CNV. They should also be educated about the need for prompt notification to an ophthalmologist who can confirm if the new symptoms are from CNV and who can begin treatment if indicated.

Follow-up examinations of patients at increased risk of visual loss or of progression to advanced AMD may facilitate the following: (1) they may permit early detection of asymptomatic but treatable neovascular lesions, which might improve the visual outcome; (2) they provide an opportunity to update the patient’s education on preventive regimens; and (3) they can reinforce the need for self-monitoring and the need for prompt evaluation for new symptoms. For patients with no risk factors for AMD, a comprehensive medical eye evaluation performed every 2 to 4 years for patients between ages 40 and 54 years, every 1 to 3 years for patients between ages 55 and 64 years, and every 1 to 2 years for patients 65 and older seems to offer a reasonable approach for detection. Patients who check monocular near vision (reading/Amsler grid) may be more likely to become aware of subtle visual symptoms due to CNV, increasing the likelihood of detecting CNV at a treatable stage. Patients with neovascular AMD report a substantial decline in quality of life and increased need for assistance with activities of daily living, which progressed as visual acuity worsened. Early detection and treatment of AMD to arrest the deterioration in vision would preserve patients’ quality of life and independence.

A clinical trial is under way to evaluate the efficacy of lutein and fish oil in the prevention of progression of advanced AMD. The Age-Related Eye Disease Study 2 has enrolled 4000 patients with non-neovascular AMD consisting of large drusen in both eyes or advanced AMD in one eye and large drusen in the fellow eye. The goal of this trial is to evaluate the effect of dietary xanthophylls (lutein and zeaxanthin) and/or omega-3 long chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) on progression to advanced AMD. Information on this trial is available at http://www.areds2.org. The AREDS formulation will be offered to all participants, because they have at least intermediate AMD. A secondary randomization in AREDS2 will evaluate the possibility of eliminating and/or lowering the amount of zinc in the AREDS formulation.

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, with particular attention to those aspects relevant to AMD.
History
An initial history should consider the following elements:
- Symptoms\textsuperscript{115 [A:II]}
  - Metamorphopsia
  - Decreased vision
- Medications and nutritional supplements\textsuperscript{[B:III]}
- Ocular history\textsuperscript{7,116,117 [B:II]}
- Medical history\textsuperscript{7,116,117 [B:II]} (including any hypersensitivity reactions)\textsuperscript{92,105}
- Family history, especially family history of AMD\textsuperscript{63,118 [B:II]}
- Social history, especially smoking\textsuperscript{24-28 [B:II]}

Examination
- Stereoscopic biomicroscopic examination of the macula\textsuperscript{[A:III]}
  Binocular slit-lamp biomicroscopy of the ocular fundus is often necessary to detect subtle clinical clues of CNV. These include small areas of hemorrhage, hard exudates, subretinal fluid, or pigment epithelial elevation.

Diagnostic Tests
Fluorescein Angiography
Intravenous fundus fluorescein angiography is indicated\textsuperscript{109,111,112 [A:II]} when the patient complains of new metamorphopsia or has unexplained blurred vision, and/or when clinical examination reveals elevation of the RPE or retina, subretinal blood, hard exudates, or subretinal fibrosis and in the following situations:
- 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 also used as a guide to direct treatment.
- To detect persistent or recurrent CNV following treatment.
- 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.\textsuperscript{109,111,112 [A:II]} Extrafoveal or juxtafoveal lesions can extend rapidly, causing irreversible damage, and subfoveal lesions may grow too large, precluding any treatment benefit.\textsuperscript{119,120}
If fluorescein angiography is to be performed, the physician must be aware of potential risks associated with this procedure\textsuperscript{121,122}; severe medical complications may occur, including death (approximately 1 in 200,000 patients). Each angiographic facility should have in place a care plan or an emergency plan and a clear protocol to minimize the risks and to manage any complications.\textsuperscript{[A:III]}

Optical Coherence Tomography
Optical coherence tomography is helpful in determining the presence of subretinal fluid and in documenting the degree of retinal thickening.\textsuperscript{123} Optical coherence tomography offers a unique ability to define cross sectional architecture of the retina that is not possible with any other imaging technology and may assist in evaluating the response of the retina and RPE to therapy by allowing structural changes to be followed accurately.\textsuperscript{124-127} Advances in optical coherence tomography (e.g., spectral domain) may allow increased resolution.
**Fundus Photography**

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

**Indocyanine Green**

Indocyanine green video-angiography is a technique that allows viewing of the choroidal circulation. The value of this test in evaluating and treating AMD remains unknown.\(^\text{128}\) It may prove useful in evaluating certain types of AMD, such as pigment epithelial detachment, poorly defined CNV, and lesions such as retinal angiomatous proliferation or polypoidal choroidal vasculopathy.\(^\text{81,129}\) Without indocyanine green, polypoidal choroidal vasculopathy may be identified as neovascular AMD, particularly in patients of African or Asian descent.\(^\text{8,530}\)

**TREATMENT**

Management options for AMD include observation, antioxidant vitamin and mineral supplements, intravitreal injection of anti-VEGF agents, PDT, and laser photocoagulation surgery.

Patients who are currently smoking should be advised to stop\(^\text{131,132}\) because there are observational data that support a causal relationship between smoking and AMD\(^\text{24,25,27,28,133}\) and other considerable health benefits of smoking cessation. Studies have found that a physician’s advice to stop smoking is a helpful motivator for patients who are attempting to quit\(^\text{131}\) and is associated with increased long-term smoking abstinence rates.\(^\text{132}\)

**Indications for Treatment**

Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4A and Table 4B, respectively. The criteria for treatment of AMD and the techniques of therapy are described in the ranibizumab, bevacizumab, pegaptanib sodium, TAP, VIP, MPS, and AREDS literature. Ranibizumab and pegaptanib sodium injection product labeling and other literature discuss techniques of intravitreal injection.\(^\text{92,105,134}\)

As is the case with most clinical trials, the AMD treatment trials described do not provide clear guidance for the management of all patients that will be encountered in clinical practice.

The risks, benefits, complications, and alternatives of the treatment should be discussed with the patient and informed consent obtained.\(^\text{135}\)

The following therapies are being evaluated in either randomized or nonrandomized clinical trials. There is insufficient evidence to guide treatment recommendations at this time.

- Other pharmacologic therapy, especially additional angiogenic inhibitors
- Photodynamic therapy combined with pharmacologic therapy
- Macular translocation surgery
- Adjunctive use of intravitreal corticosteroids with verteporfin PDT
- Radiotherapy with strontium (Cabernet study)
### TABLE 4A  TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR NON-NEOVASCULAR AMD

<table>
<thead>
<tr>
<th>Recommended Treatment</th>
<th>Diagnoses Eligible for Treatment</th>
<th>Follow-up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervals</td>
</tr>
<tr>
<td>Observation with no medical or surgical therapies(^{7,77,125,127})</td>
<td>Early AMD (AREDS category 2)</td>
<td>Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV(^{124,126})</td>
</tr>
<tr>
<td>Advanced AMD with bilateral subfoveal geographic atrophy or disciform scars</td>
<td></td>
<td>Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV(^{124,126})</td>
</tr>
<tr>
<td>Antioxidant vitamin and mineral supplements as recommended in the AREDS reports(^{124,126})</td>
<td>Intermediate AMD (AREDS category 3)</td>
<td>Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV(^{124,126})</td>
</tr>
<tr>
<td>Advanced AMD in one eye (AREDS category 4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### TABLE 4B  TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR NEOVASCULAR AMD

<table>
<thead>
<tr>
<th>Recommended Treatment</th>
<th>Diagnoses Eligible for Treatment</th>
<th>Follow-up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab intravitreal injection 0.5 mg as recommended in ranibizumab literature(^{102,126})</td>
<td>Subfoveal CNV</td>
<td>Patients should be instructed to report promptly 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(^{102,126})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Return exam approximately 4 weeks after treatment; subsequent follow-up depends on the clinical findings and judgment of the treating ophthalmologist(^{102,126})</td>
</tr>
<tr>
<td>Bevacizumab intravitreal injection as described in published reports(^{104,105})</td>
<td>Subfoveal CNV</td>
<td>Patients should be instructed to report promptly 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(^{104,105})</td>
</tr>
<tr>
<td>The ophthalmologist should provide appropriate informed consent with respect to the off-label status.(^ {107})</td>
<td></td>
<td>Return exam approximately 4 to 8 weeks after treatment; subsequent follow-up depends on the clinical findings and judgment of the treating ophthalmologist(^{104,105})</td>
</tr>
</tbody>
</table>
Complications of Treatment

Possible complications of the four main modalities of treatment for AMD are listed below.

**Intravitreal Pharmacotherapy**
- Ranibizumab injection
  - **Endophthalmitis** (cumulative ≤1.0% over 2 years in MARINA study; <1.0% over 1 year in ANCHOR study)\(^\text{142,143}\)
  - Retinal detachment (<0.1% of treated cases during the first year of treatment)\(^\text{142,143}\)
  - Traumatic injury to the lens (0.1% of treated cases during the first year of treatment)\(^\text{142,143}\)

In addition to those listed above, other adverse events reported more frequently in the group treated with ranibizumab injection compared with the control group were conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure within 60 minutes of injection, and intraocular inflammation. During the first year of the ANCHOR and MARINA trials, myocardial infarction and stroke rates were higher in the 0.5 mg group than in the control group (2.9% and 1.3%, respectively); these differences were not statistically significant and were not evident at 2-year follow-up.\(^\text{142,143}\)

- Bevacizumab injection
  - Reported safety data are limited by short and variable follow-up periods and differences in reporting criteria
  - Reported ocular adverse events include bacterial endophthalmitis (0.16%), tractional retinal detachments (0.16%), uveitis (0.09%), rhegmatogenous retinal detachment (0.02%), and vitreous hemorrhage (0.16%)\(^\text{144}\)

This treatment has not been evaluated in randomized controlled trials.
Pegaptanib sodium injection
- 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)

In addition to the adverse events listed above, other events reported more frequently in the group treated with pegaptanib sodium injection compared with the control group were eye pain, vitreous floaters, punctate keratitis, vitreous opacities, cataract, anterior chamber inflammation, visual disturbance, eye discharge, and corneal edema.

Verteporfin Photodynamic Therapy
- Severe vision loss occurred within 1 week following treatment in 1% to 4% of patients, and may be permanent
- Infusion site extravasation
- Idiosyncratic back pain occurred during infusion of the drug in 1% to 2% of patients
- Photosensitivity reaction occurred in less than 3% of patients. (This can be prevented by avoiding direct sunlight.)

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, breast-feeding, 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
- RPE rips (tears)
- Treatment of the fovea in juxtafoveal neovascularization

Introduction or enlargement of a pre-existing scotoma, with or without visual acuity loss, is not a complication of thermal laser photocoagulation surgery; 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
  - Increased yellowing of the skin (8.3% compared with 6.0%, \( P=0.008 \))
  - Increased risk of developing lung cancer in current smokers or former smokers who stopped within the last year
- Zinc
  - Increased risk of hospitalizations for genitourinary causes (7.5% in those treated with zinc compared with 4.9% in those not treated with zinc, \( P=0.001 \))
  - Copper deficiency anemia (concomitant administration of copper is necessary)

When considering long-term supplementation, some people may have reason to avoid one or more of the supplements evaluated in the AREDS. 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 AREDS should be reviewed by the patient’s primary care physician.
FOLLOW-UP

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

History

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

- Symptoms, including decreased vision and metamorphopsia\textsuperscript{115} [A:II]
- Changes in medications and nutritional supplements\textsuperscript{[B:III]}
- Changes in medical and ocular history\textsuperscript{[B:III]}
- Changes in social history (smoking)\textsuperscript{[B:II]}

Examination

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

- Visual acuity\textsuperscript{[A:III]}
- Stereoscopic biomicroscopic examination of the fundus\textsuperscript{[A:III]}

Diagnostic tests used in the follow-up examination are identical to those listed under Diagnosis, and the treatment plan is identical to the one described under Treatment.

Follow-up after Treatment for Neovascular AMD

In addition to the above recommendations, patients who have been treated with ranibizumab, bevacizumab, or pegaptanib sodium injection; verteporfin PDT; or thermal laser photocoagulation surgery should be examined at regular intervals by means of biomicroscopy of the fundus.\textsuperscript{[A:III]} Optical coherence tomography,\textsuperscript{125} [A:III] fluorescein angiography,\textsuperscript{109,111,112} [A:I] and fundus photography\textsuperscript{[A:III]} may be helpful to detect signs of exudation and should be used when clinically indicated.

Patients treated with ranibizumab injection should have follow-up examinations approximately 4 weeks following the treatment.\textsuperscript{145} [A:II] Subsequent follow-up is dependent on the clinical findings and judgment of the treating ophthalmologist. Patients treated with bevacizumab injection should have follow-up examinations approximately 4 to 8 weeks following the treatment.\textsuperscript{[A:III]} Patients treated with pegaptanib sodium injection should have follow-up examinations approximately 6 weeks following the treatment.\textsuperscript{[A:III]}

Subsequent examinations, optical coherence tomography, and fluorescein angiography should be performed as indicated depending on the clinical findings and the judgment of the treating ophthalmologist.\textsuperscript{[A:III]} Treated patients should be instructed to report symptoms of endophthalmitis and should be re-examined promptly.\textsuperscript{[A:III]}

Follow-up examinations and fluorescein angiograms have been recommended at least every 3 months for up to 2 years following verteporfin PDT treatment for subfoveal CNV.\textsuperscript{138,139}

Fellow Eye

For patients with unilateral disease, the fellow eye without CNV remains at high risk of developing advanced AMD.\textsuperscript{146} The risk can be substantially lowered over a 5-year period by taking the AREDS supplements.\textsuperscript{1} 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.\textsuperscript{[A:III]} 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 in an effort to detect asymptomatic CNV at a treatable stage.
PROVIDER
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 data collection may be conducted by other trained individuals under the ophthalmologist's supervision.

PHYSICIAN QUALITY REPORTING INITIATIVE PROGRAM
The Physician Quality Reporting Initiative (PQRI) program, initially launched by the Centers for Medicare and Medicaid Services in July 2007, encourages quality improvement through the use of clinical performance measures on a variety of clinical conditions. A measure in the 2008 PQRI program for AMD is dilated macular examination, including documentation of the presence or absence of macular thickening or hemorrhage and the level of AMD severity. A measure proposed for the 2009 PQRI program is counseling of patients with AMD about the risks and benefits of the AREDS supplements.

COUNSELING/REFERRAL
All patients with AMD should be educated about the prognosis of the disease and the potential value of treatment as appropriate for their ocular and functional status. Patients can be told that although central visual loss is common, total visual loss is rare. Patients with AMD can be reassured that there is no harm in using their eyes, and they may be told that the effect of light and other factors on vision remains uncertain.

The informed consent process should include 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.

Vision rehabilitation restores functional ability and patients with reduced visual function should be referred for vision rehabilitation and social services. Patients with severe visual loss related to AMD who are referred for vision rehabilitation services often have unrealistic expectations. Special optical or electronic magnifying lenses, bright lights, and other reading aids may help patients to read more effectively, but not as well as they did before the onset of AMD. More information on vision rehabilitation, including materials for patients, is available at http://www.aoa.org/smartsight.

Loss of visual acuity increases the risk of frequent falls. Depression and visual hallucinations (Charles Bonnet syndrome) are frequent accompaniments of severe central vision loss. Patients with Charles Bonnet syndrome and their family members should be informed that visual symptoms are not unusual and not 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.
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 respond in an adequate and timely manner.

- The ophthalmologist maintains complete and accurate medical records.
- On appropriate request, the ophthalmologist provides and 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. SUMMARY OF MAJOR RECOMMENDATIONS FOR CARE

DIAGNOSIS

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

History

An initial history should consider the following elements:

- Symptoms\(^2\)[A:II]
  - Metamorphopsia
  - Decreased vision
- Medications and nutritional supplements\(^[B:III]\)
- Ocular history\(^3,5\)[B:II]
- Medical history\(^3,5\)[B:II] (including any hypersensitivity reactions)\(^6,7\)
- Family history, especially family history of AMD\(^8,9\)[B:II]
- Social history, especially smoking\(^10-14\)[B:II]

Examination

- Stereoscopic biomicroscopic examination of the macula\(^[A:III]\)

TREATMENT

Management options for AMD include observation, antioxidant vitamin and mineral supplements, intravitreal injection of anti-VEGF agents, PDT, and laser photocoagulation surgery.

Patients who are currently smoking should be advised to stop\(^15,16\)[A:II] because there are observational data that support a causal relationship between smoking and AMD\(^10,11,13,14,17\)[A:II] and other considerable health benefits of smoking cessation. Studies have found that a physician’s advice to stop smoking is a helpful motivator for patients who are attempting to quit\(^15\) and is associated with increased long-term smoking abstinence rates.\(^16\)

Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4A and Table 4B, respectively, in the main body of the text.

The risks, benefits, complications, and alternatives of the treatment should be discussed with the patient and informed consent obtained.\(^18\)[A:III]

FOLLOW-UP

A history and examination are the recommended elements of the follow-up visits. Recommended follow-up intervals are listed in Tables 4A and 4B in the main body of the text.

History

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

- Symptoms, including decreased vision and metamorphopsia\(^2\)[A:II]
- Changes in medications and nutritional supplements\(^[B:III]\)
- Changes in medical and ocular history\(^3,5\)[B:III]
- Changes in social history (smoking)\(^10-14\)[B:II]
Examination

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

- Visual acuity[A:III]
- Stereoscopic biomicroscopic examination of the fundus[A:III]

Follow-up after Treatment for Neovascular AMD

In addition to the above recommendations, patients who have been treated with ranibizumab, bevacizumab, or pegaptanib sodium injection; verteporfin PDT; or thermal laser photocoagulation surgery should be examined at regular intervals by means of biomicroscopy of the fundus[A:III]. Optical coherence tomography, visual field testing, fluorescein angiography, and fundus photography[A:III] may be helpful to detect signs of exudation and should be used when clinically indicated.

Patients treated with ranibizumab injection should have follow-up examinations approximately 4 weeks following the treatment. Subsequent follow-up is dependent on the clinical findings and judgment of the treating ophthalmologist. Patients treated with bevacizumab injection should have follow-up examinations approximately 4 to 8 weeks following the treatment. Patients treated with pegaptanib sodium injection should have follow-up examinations approximately 6 weeks following the treatment.[A:III]

Subsequent examinations, optical coherence tomography, and fluorescein angiography should be performed as indicated depending on the clinical findings and the judgment of the treating ophthalmologist.[A:III] Treated patients should be instructed to report symptoms of endophthalmitis and should be re-examined promptly.[A:III]

Follow-up examinations and fluorescein angiograms have been recommended at least every 3 months for up to 2 years following verteporfin PDT treatment for subfoveal CNV.24,25

COUNSELING/REFERRAL

All patients with AMD should be educated about the prognosis of the disease and the potential value of treatment as appropriate for their ocular and functional status.[A:III]

Vision rehabilitation restores functional ability and patients with reduced visual function should be referred for vision rehabilitation and social services. More information on vision rehabilitation, including materials for patients, is available at [http://www.aoa.org/smartsight](http://www.aoa.org/smartsight).

REFERENCES

APPENDIX 3. NEOVASCULAR AMD TREATMENT TRIALS

RANIBIZUMAB

Ranibizumab intravitreal injection for the treatment of all subtypes of neovascular age-related macular degeneration (AMD) received Federal Drug Administration (FDA) approval in June 2006 based on the results of three randomized controlled trials. The MARINA study enrolled 716 patients with minimally classic and occult lesions; the treatment group received a mean of 22 total ranibizumab injections (0.3 mg or 0.5 mg) through 24 months. The ANCHOR study enrolled 423 patients with predominantly classic lesions and compared ranibizumab injection with verteporfin photodynamic therapy (PDT); data are available for 12 months of treatment. Patients in the treatment group received 0.3 mg or 0.5 mg ranibizumab injections monthly. The PIER study enrolled 184 patients with or without a classic component; treated patients received ranibizumab injections (0.3 mg or 0.5 mg) once a month for 3 consecutive doses, followed by a dose administered once every 3 months. The FDA recommended dosage of ranibizumab is 0.5 mg by intravitreal injection once a month.

At 12 months, approximately 95% of patients in the MARINA and ANCHOR studies who received ranibizumab injections maintained their visual acuity, defined as losing fewer than 15 letters of visual acuity, compared with approximately 62% of the control arm patients. At 24 months, 90% of treated patients in the MARINA study lost less than 15 letters of visual acuity; 33% gained 15 or more letters of visual acuity (P<0.01). In the ANCHOR study, 96% of patients treated with ranibizumab injection maintained visual acuity at 12 months compared with 64% of the verteporfin PDT group. Forty percent of the group treated with ranibizumab injection gained 15 or more letters in visual acuity compared with 6% of the verteporfin PDT treatment group (P<0.01). Patients treated with ranibizumab injection in the PIER study had an initial increase in visual acuity and then, on average, lost visual acuity, returning to baseline at 12 months.

PEGAPTANIB SODIUM

Pegaptanib sodium intravitreal injection for the treatment of all subtypes of neovascular AMD received FDA approval in December 2004 based on results from the VEGF Inhibition Study in Ocular Neovascularization (VISION) trial. The VISION trial was designed as two concurrent randomized double-masked clinical trials; 1,208 patients received either pegaptanib sodium injection (0.3 mg, 1.0 mg, or 3.0 mg) or a sham injection into one eye every 6 weeks for a total of 48 weeks. Patients eligible for the trial were 50 years old or older, and they had subfoveal choroidal neovascularization (CNV) related to AMD and a best corrected visual acuity of 20/40 to 20/320 in the study eye. The CNV included classic, minimally classic, and occult types. Patients enrolled in the trials were allowed one verteporfin PDT before the study start and any number of verteporfin PDT treatments throughout the study period at the discretion of the investigator. This study protocol ensured that pegaptanib sodium injection was administered to patients who were already receiving usual care. The groups treated with pegaptanib sodium injection 0.3 mg exhibited a statistically significant result in both trials for the primary efficacy endpoint at 1 year. On average, patients treated with pegaptanib 0.3 mg and sham-treated patients continued to experience vision loss. However, the rate of vision decline in the pegaptanib-treated group was slower than the rate in the patients who received sham treatment. Seventy percent of patients treated with pegaptanib sodium injection (0.3 mg, n = 294) lost fewer than 15 letters of visual acuity compared with 55% in the control group (n = 296) (P<0.001). Ten percent of patients treated with pegaptanib sodium injection (0.3 mg, n = 294) had severe visual acuity loss (30 letters or more) compared with 22% in the control group (n = 296) (P<0.001). The beneficial effect was seen for all types of neovascularization.

VERTEPORFIN PHOTODYNAMIC THERAPY

Photodynamic therapy with verteporfin has FDA approval for the treatment of predominantly classic subfoveal CNV. In a verteporfin PDT study (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy [TAP]), a treatment benefit was evident at both 1
and 2 years following randomization. Subfoveal lesions of up to 5400 microns in the greatest linear diameter were enrolled in these trials, and prerandomization visual acuity ranged from an approximate Snellen equivalent of 20/40 to 20/200. Treatment benefit was seen for the treated group as a whole. At the month 24 examination, 213 of 402 verteporfin-treated patients (53%) compared with 78 of 207 placebo-treated patients (38%) lost fewer than 15 letters of visual acuity (P<0.001). In the subgroup analyses for predominantly classic lesions at baseline (in which the area of classic CNV made up at least 50% of the area of the entire lesion), 94 of 159 verteporfin-treated patients (59%) compared with 26 of 83 placebo-treated patients (31%) lost fewer than 15 letters of visual acuity at the month 24 examination (P<0.001). For minimally classic lesions at baseline (in which the area of classic CNV made up less than 50% but more than 0% of the area of the entire lesion), no statistically significant differences in visual acuity were noted.\textsuperscript{138,139} Based on these subgroup analyses, treatment recommendations were made for the predominantly classic lesions even though a beneficial effect was found in the group overall.

The Verteporfin in Photodynamic Therapy (VIP) study indicates that PDT with verteporfin in eyes with subfoveal lesions composed of occult but no classic CNV with presumed recent disease progression can reduce the risk of moderate and severe visual acuity loss, particularly if the lesions are relatively small (<4 Macular Photocoagulation Study [MPS] disc areas) or the visual acuity is relatively low (an approximate Snellen equivalent of worse than 20/50).\textsuperscript{140} At 24 months, 29% of verteporfin-treated eyes compared with 47% of placebo-treated eyes lost 30 letters (six lines) or more of vision (P=0.004).

It should be noted that although both the TAP study and the VIP study were conducted with retinal specialists who are familiar with the fluorescein angiographic findings of the spectrum of occult and classic features of CNV, in both studies cases were enrolled that did not meet the eligibility requirements. This indicates the difficulty in distinguishing the various kinds of lesions. Another factor that may be considered as a guideline for treatment may be lesion size.\textsuperscript{141} For example, an analysis of treatment outcomes by lesion size following PDT from the TAP study and VIP study suggested that therapy might reduce the risk of vision loss in small, minimally classic lesions.\textsuperscript{152}

**THERMAL LASER PHOTOCOAGULATION SURGERY**

Thermal laser photocoagulation surgery was studied in the MPS, a randomized controlled multicenter study to evaluate the efficacy of this treatment for CNV.\textsuperscript{109-112} The majority of CNV recurrences after photocoagulation treatment occur within the first year, after which there is a slow increase over the next 3 to 4 years. The MPS reported a 5-year persistence/recurrence rate of 54% for the extrafoveal study, a 4-to-5-year rate of 78% for the juxtafoveal study, and a 3-year rate of 56% for the subfoveal study. More than 90% of recurrences are on the foveal side following laser surgery of extrafoveal and juxtafoveal CNV.\textsuperscript{109,110,112} Introduction of a scotoma or enlargement of a pre-existing scotoma, with or without visual acuity loss, is an immediate and permanent effect of photocoagulation surgery.

Because of the loss of vision associated with laser photocoagulation surgery (82% of treated patients end up with visual acuity worse than 20/200), photocoagulation is no longer the first treatment of choice for subfoveal neovascularization.
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 (AREDS 2): An ongoing 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 will be offered the AREDS supplements. A secondary randomization evaluates 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 visual acuity 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.

Apheresis: Apheresis with membrane differential filtration is a form of plasmapheresis that has been investigated for treatment of AMD. A clinical trial of this therapy in the United States has been suspended (NCT00460967) [http://www.clinicaltrials.gov].

AREDS: See Age-Related Eye Disease Study.

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.

Cabernet Study: Study of strontium 90 beta radiation with ranibizumab to treat age-related macular degeneration.

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.

CNV: See Choroidal neovascularization.

DA: See Disc area.
**DENALI Study:** Part of the SUMMIT studies, this trial compares ranibizumab and verteporfin PDT combination therapy with ranibizumab alone.

**Disc area (DA):** As defined by the Macular Photocoagulation Study, the area of a circle with a diameter of 1.5 millimeters (1500 microns) 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 microns in diameter, intermediate if they are greater than or equal to 63 and less than or equal to 125 microns, and large when the diameter is greater than 125 microns, and they may be considered soft if they have ill-defined edges.

**Extrafoveal choroidal neovascularization:** A choroidal neovascular membrane that comes no closer than 200 microns 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.


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

**LEVEL Study:** Study of the safety and efficacy of pegaptanib as a maintenance therapy in patients with neovascular AMD who have had improvement of their disease after recent treatment.

**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.
OCT: See optical coherence tomography.

Optical coherence tomography: 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.

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 (VEGF165) 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.

PIER Study: A phase IIIb multicenter randomized double-masked sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal neovascularization with or without classic CNV.

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.

Polypoidal choroidopathy: Characterized by multiple and recurrent serosanguineous RPE detachments, which often resemble hemorrhagic detachment in AMD.

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.

RAP: See Retinal angiomatosus proliferation.

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.

Retinal angiomatosus proliferation (RAP): Characterized by proliferation of retinal capillaries in the paramacular area that may present as intraretinal, subretinal, or choroidal neovascularization.

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.

**SUMMIT**: Two studies, called Denali in North America and Mont Blanc in Europe, that compare ranibizumab and verteporfin PDT combination therapy with ranibizumab alone.

**TAP Study**: Treatment of Age-Related Macular Degeneration with Photodynamic Therapy study.

**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.

**VERITAS Study**: Verteporfin Intravitreal Triamcinolone Acetonide Study.

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

**VIP Study**: Verteporfin in Photodynamic Therapy study.

**VISION Study**: VEGF Inhibition Study in Ocular Neovascularization (using pegaptanib [Macugen]).

**VisTA Study**: Visudyne with Intravitreal Triamcinolone Acetonide study.

**Well-defined choroidal neovascularization**: CNV with classic or occult features that has well-demarcated boundaries on fluorescein angiography.

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**RELATED ACADEMY MATERIALS**

**Basic and Clinical Science Course**
- Retina and Vitreous (Section 12, 2008-2009)

**Complementary Therapy Assessments**
- Antioxidant Supplements and Age-Related Macular Degeneration (2002)
- Apherens for Age-Related Macular Degeneration (2003)

**Eye Fact Sheets**
- Age-Related Macular Degeneration (AMD) and Nutritional Supplements (2007)
- Age-Related Macular Degeneration (AMD) and Nutritional Supplements (Spanish: La Degeneración Macular y Nutrición (2005)
- Fluorescein Angiography (2005)
- Fluorescein and ICG Angiography (2004)
- Photodynamic Therapy for Age-Related Macular Degeneration (2005)

**Focal Points**
- Optical Coherence Tomography in the Management of Retinal Disorders (2006)
REFERENCES


