# AGE RELATED MACULAR DEGENERATION (AMD)
# PREFERRED PRACTICE PATTERNS (PPP) Philippines: 2016

**The Age Related Macular Degeneration (AMD) Preferred Practice Patterns (PPP) Philippines: 2016 was prepared by the VitreoRetina Society of the Philippines (VRSP) for the Philippine Academy of Ophthalmology (PAO) Preferred Practice Patterns (PPP) of selected eye diseases.**

**The AMD PPP Philippines: 2016 was adapted from the American Academy of Ophthalmology (AAO) PPP for Age Related Macular Degeneration updated 2015.[1]**

**The DR PPP Philippines: 2016 was reviewed and edited through e-mail correspondence by a Panel of Experts with interest in this condition. The panel then convened to draft the current manuscript.**

**This PPP will be updated on an ongoing basis.**

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# AGE-RELATED MACULAR DEGENERATION (AMD) PREFERRED PRACTICE PATTERNS (PPP) Philippines: 2016

## Preferred Practice Patterns (PPP)

The Preferred Practice Patterns (PPP) for Age Related Macular Degeneration (AMD) was adapted from the American Academy of Ophthalmology (AAO).[1] Each was determined by a Panel of Experts composed of VitreoRetina Society (VRSP) members to be clinically relevant and specific enough to provide useful information to practitioners.

Preferred Practice Patterns (PPP) aim to provide guidance to practitioners for patient care. They do not aim to provide standards for the care of a particular individual. PPP cannot meet the needs of all patients. Adherence to these PPP's will not ensure a successful outcome in every situation. It may be necessary to approach each patient's needs in different ways. The physician must make the ultimate decisions about the propriety of the care of every patient weighing all the circumstances presented.

The PPP are not medical standards to be adhered to in all individual situations. The Philippine Academy of Ophthalmology (PAO) 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.

It is essential to recognize that true medical excellence is achieved only when skills are applied in such a manner that patients' needs are the foremost consideration.

This PPP is designed to be a working document and will be updated on an ongoing basis.

## HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE[1]

Increasing age and genetic factors are risk factors for the development of advance AMD. Cigarette smoking has also been identified in numerous studies and is the main modifiable risk factor. Cessation of smoking is strongly recommended when advising patients with AMD or at risk for AMD.

In patients with intermediate or advanced age-related macular degeneration, supplementation with the original Age-Related Eye Disease Study (AREDS) and AREDS2 antioxidant vitamins and minerals should be considered. There is no evidence to support the intake of these supplements in patients who have less than intermediate AMD.

Early detection and immediate treatment may improve visual outcome in patients with neovascular AMD. Progression to advanced AMD in the fellow eye is reduced with the use of AREDS2 supplements.

New cases and recurring AMD may be detected by fundus photo, fluorescein angiography and optical coherence tomography (OCT). These diagnostic tests will also guide treatment.

The first line and most effective method of treatment for neovascular AMD is the intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab).

Adverse events such as infectious endophthalmitis, related to the intravitreal injection of anti-VEGF agents, are rare. Symptoms suggesting the development of post-injection endophthalmitis or retinal detachment require prompt evaluation.

## Age Related Macular Degeneration (AMD)

**DISEASE DEFINITION**

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

- Presence of at least intermediate-sized drusen (63 um or larger in diameter)
- Retinal pigment epithelial (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- Reticular pseudodrusen (subretinal drusenoid deposits)
- Presence of any one of the following features: geographic atrophy of the RPE, choroidal neovascularization (exudative, wet), polypoidal choroidal vasculopathy, or retinal angiomatous proliferation

The Preferred Practice Patterns (PPP) of the American Academy of Ophthalmology (AAO) uses the classification of the Age-Related Eye Disease Study (AREDS).[2] This classification defines the early and intermediate stages of AMD since current treatment recommendations are based on these classifications.

The AREDS was conducted between 1992 and 2006. It was a prospective multicenter randomized clinical trial designed to assess the risk factors and natural course of age-related cataract and AMD. The effects of antioxidant vitamins and minerals on age-related cataract and AMD were also studied.

The AREDS classification of AMD is as follows:[3]

- No AMD (AREDS category 1): is characterized by no or few small drusen (<63 um in diameter)
- Early AMD (AREDS category 2): is characterized by a combination of multiple small drusen, few intermediate drusen (63-124 um), or mild RPE abnormalities
- Intermediate AMD (AREDS category 3): is characterized by any one of the following features:
    - Numerous intermediate drusen
    - At least one large drusen (125 um or larger 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 features in one eye
    - Geographic atrophy of the RPE involving the foveal center
    - Neovascular maculopathy that includes the following:
        - Choroidal neovascularization (CNV) defined as pathologic angiogenesis originating from the choroidal vasculature that extends through the Bruch's membrane
        - Serous and or hemorrhagic detachment of the neurosensory retina or RPE
        - Retinal hard exudates (a secondary phenomenon resulting from chronic intravascular leakage)
        - Subretinal and sub-RPE fibrovascular proliferation
        - Disciform scar (subretinal fibrosis)

**PATIENT POPULATION**

Patients with AMD may or may not present with visual symptoms. Typically, the patients are 50 years old or older.

**CLINICAL OBJECTIVES**

- Identify patients at risk for visual loss due to AMD
- Educate patients and their families about the disease, risk factors and preventive measures
- Minimize or reverse visual loss and resultant functional impairment through early detection, self-monitoring, timely treatment and regular follow-up evaluations
- Advice patients regarding resources and expertise related to visual rehabilitation

## BACKGROUND

**PREVALENCE**

Age-related macular degeneration (AMD) may result in severe and irreversible vision impairment .[4-6]

The United States data estimates that 3 million patients will be affected by advanced AMD in at least one eye by year 2020.[7] These estimates will be affected by more effective treatments for neovascular AMD using anti-vascular endothelial growth factor (VEGF) agents and by the use of antioxidant vitamins with zinc to slow down the progression of the disease. Studies in the United States estimate the anti-VEGF agents may reduce the odds of legal blindness from neovascular AMD by as much as 70% in 2 years.[8] USA data further estimate that the use of anti-oxidant vitamins (e.g. vitamin C, Vitamin E), lutein, zeaxanthin, and zinc may reduce progression to the more advanced stages of AMD by approximately 25% at 5 years.[3,8]

AMD is a disease spectrum with early and late stages. Although, the onset of AMD is considered by most to occur at age 50 years, the early stages of AMD may be detected between the ages of 40-50 years. The incidence and progression of AMD and most associated features (e.g., drusen) increase with increasing age.

Approximately 80% of AMD patients have the non-neovascular or atrophic form of AMD[5], 90% of severe visual acuity loss (20/200 or worse) is due to the neovascular form.[9]

**RISK FACTORS**

Increasing age is the main risk factor for the development of AMD. Among the many modifiable risk factors that have been investigated, cigarette smoking has been consistently identified in several studies. Patients should be strongly advised to stop smoking.[10-19] It is important to realize that the risk factors have not been shown to be causative of AMD.

**Smoking, Hypertension and Cardiovascular Disease**

The relative risk for AMD increases with an increase in number of smoking pack-years. [15-20] The risk of developing AMD in individuals who have stopped smoking for more than 20 years is comparable to the risk in non-smokers.[12] Thus, it is strongly recommended that smoking be stopped in advising patients as it is a key modifiable risk factor. Studies that assessed the relationship between AMD, hypertension and other cardiovascular diseases have shown conflicting results.[21,22-28]

**Levels of Antioxidants**

Low levels of antioxidants have been included in the list of additional risk factors for developing AMD. However, low plasma and dietary levels of antioxidants e.g. vitamin C and E, carotenoids (lutein and zeaxanthin) and zinc have not been consistently shown to be risk factors for AMD.[29-35]

Oral antioxidant vitamins (vitamin C, E, beta-carotene) and zinc supplementation at high doses were demonstrated by the original AREDS results to have a beneficial effect in reducing the progression of advanced AMD or intermediate AMD in the fellow eye to advanced AMD.[36] However, Vitamin E supplementation should not go above the level used in the AREDS study.[37]

The AREDS2 replaced beta-carotene (used in the original AREDS) with lutein/zeaxanthin.[38] The removal of beta-carotene may decrease the observed increased mortality among smokers, who were observed to have a higher incidence of lung cancer associated with the use of supplemental beta-carotene.[38]

Lastly, the AREDS2 results demonstrated that reducing zinc dose (from 80 mg to 25 mg) or adding an omega-3 polyunsaturated fatty acid supplement (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA}) had no effect on the progression of AMD.[38]

**Diet**

Dietary fat intake has been associated with advanced AMD.[13,39-44] Likewise, 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.[17]

A high dietary intake of foods rich in omega-3-long-chain polyunsaturated fatty acids, such as fish has been associated with a reduced risk of AMD.[23,43-46]

In the AREDS study, patients who were at moderate risk for progression of AMD were found to be 30% less likely to develop advanced AMD after 12 years if they had a high dietary intake of omega-3 (not in the form of a supplement).[44] Despite this dietary association, oral supplements with DHA and EPA (omega-3-unsaturated fatty acids) were not shown to have any benefit in the AREDS report.

**Genetic Factors**

Molecular genetic studies and epidemiologic studies have determined some of the genetic factors in AMD.[47-53] An association of the complement factor H (CFH) Y2O2H polymorphism with a higher risk of AMD was demonstrated by several studies in 2005.[54-59] The ARMS2/HtrA1 genes are in close disequilibrium; together, they are also strongly associated with AMD.[60-62] Other genes include the hepatic lipase (LIPC) gene and the rs3775291 variant in the toll-like receptor 3 (TLR3) gene.[63,64]

AMD has a complex genetic background with similar phenotypes. Protective genetic associations as well as some associations with disease progression and response to anti-VEGF have been reported and require further investigation.

Prospectively designed clinical trials are needed to assess the value of genetic testing in AMD.

At this time, the routine use of genetic testing is not supported by current literature.

**Other Risk Factors**

An increase in the waist/hip ratio for men has been demonstrated to increase the risk of both early and late AMD in men.[65] A higher risk of AMD progression has been associated with increased markers of C-reactive protein: a marker of inflammation. Other possible risk factors including hormonal status,[66-70] sunlight exposure,[71-73] alcohol use[74-76] and vitamins B and D status [77,78] have been studied and all have been determined to yield inconclusive findings.

## NATURAL HISTORY

**Early AMD**

The AREDS defined the categories of AMD. Early AMD (Category 2) is characterized by small drusen <63 um), a few medium/intermediate drusen (63-125 um), and/or minimally detected or no pigment epithelial abnormalities in the macula. There is a low risk of progressing to advanced AMD after 5 years in either eye.[3]

**Intermediate AMD**

Intermediate AMD (category 3) is defined by the AREDS as the presence of medium/intermediate drusen (63-124 um) or one or more large drusen (>125 um in diameter) in one or both eyes. The risk of progressing to advanced AMD after 5 years is 18% according to the original AREDS. For patients with large drusen in one eye, the rate of progression to advanced AMD is 6.3%. For those patients with multiple bilateral large drusen, the risk increases to 26% at 5 years.[3,79,80]

In 2005, a simple severity scale was developed in order to advice patients about their 5-year risk for developing advanced AMD. The scale is based on two easily identified retinal abnormalities: (1) one or more large drusen (≥ 125 um) and (2) the presence of pigmentary abnormalities.[80] The grading system from 0-4, assigns to each eye 1 risk factor for the presence of any pigment abnormality, and 1 risk factor for the presence of 1 or more large drusen. The presence of intermediate drusen in both eyes is counted as 1 risk factor. The risk factors are summed across both eyes. The approximate 5-year risk of developing advanced AMD in at least one eye increases as the score increases.

- 4 factors, 45%
- 3 factors, 26%
- 2 factors, 9%
- 1 factor, 4 %
- 0 factor, 0.5%

The reported 10-year risk is as follows:

- 4 factors, 71%
- 3 factors 53%,
- 2 factors 28%
- 1 factors 8%
- 0 factor 1.5% [84]

Using the severity scale, for eyes without large drusen, the presence of medium/intermediate drusen in both eyes is considered as **1 risk factor**.

One eye with advanced AMD is considered to have **2 risk factors**. If the same eye has concomitant large drusen and RPE pigmentary disturbances, they are considered to have **4 risk factors**. This has the highest risk for progression to advanced AMD: 50% by 5 years and 71% by 10 year.[81-84]

The presence of reticular pseudodrusen (subretinal drusenoid deposits) is best imaged using fundus autofluorescence, infrared reflectance and/or spectral domain optical coherence tomography (SD-OCT). These changes are associated with progression to the geographic atrophy or non-neovascular AMD. [82-85] (See Glossary)

The objective of this multi-center clinic-based prospective cohort study was to describe the natural history of eyes with drusenoid pigment epithelial detachments (DPED) associated with age-related macular degeneration (AMD). Among the 4757 participants enrolled in the Age-Related Eye Disease Study (AREDS), 255 were identified as having DPED in at least one eye (311 eyes). 42% of eyes with DPED progressed to

advanced AMD in 5 years (19% central geographic atrophy and 23% neovascular AMD). Among eyes that did not progress to advanced AMD, calcified drusen and pigmentary changes were prominent. 40% of eyes had visual decline (>15 letters) at year 8-9. Laser at the margin of the PED may flatten the PED.[85]

**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. Visual acuity will be affected in this category. The AREDS also reports that for patients with advanced AMD in one eye, the risk of progression to advanced AMD in the better eye is 35%-50% at 5 years.[80]

Advanced non-neovascular AMD presents with central geographic atrophy. These eyes may also present with one or more zones of well-demarcated RPE and/or choriocapillaris atrophy. The atrophic areas may be surrounded by drusen and other pigmentary abnormalities. Visual acuity loss occurs more slowly compared with neovascular AMD. Nevertheless, geographic atrophy involving the foveal center is associated with 10% of all AMD-related visual loss of 20/200 or worse.[86] Patients with geographic atrophy not affecting the central fovea may present with relatively good distance visual acuity with decreased ability to perform near tasks such as reading.[86] Choroidal neovascularization may also occur.

On fluorescein angiography, neovascular AMD is characterized 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. Other clinical features of neovascular AMD may include:

- Retinal Pigment Epithelial Detachments (RPED)
- Retinal angiomatous proliferation (RAP) [87]

Idiopathic polypoidal choroidal vasculopathy (IPCV)[88], which should be suspected in patients with orange polypoid lesions, are often located in the peripapillary region. An indocyanine green (ICG) angiogram is useful in establishing the diagnosis. IPCVs do not respond as well to anti-VEGF compared to AMD because VEGF is found in low levels in IPCV and is thus, thought to play a minor role in its pathophysiology.[89,90] It has been reported that the polyps seen in IPCVs respond poorly to ranibizumab. The EVEREST Study has shown that PDT given either alone or in combination with ranibizumab provides the best outcome in the treatment of IPCV. Currently, it is thought that IPCVs are a separate entity altogether and not a variant of AMD because their immunohistochemical characteristics differ. Moreover, 50% of neovascular AMD which are non-responsive to anti-VEGF, are eventually diagnosed as IPCV.[91] IPCVs have a higher prevalence in patients with Asian ancestry.[92]

## RATIONALE FOR TREATMENT

For the treatment of neovascular AMD, prospective randomized controlled clinical trials support the use of intravitreal injection of anti-VEGF agents, photodynamic therapy (PDT) and laser photocoagulation. To slow the progression to later stages of AMD, the use of antioxidant vitamins and minerals has been reported.

At this time, geographic atrophy, which is also known as non-neovascular AMD, has no proven treatment.

## TREATMENT MODALITIES

**Early AMD**

The AREDS reported that there is no evidence that the combination of antioxidant vitamins and minerals reduces the progression of early AMD to the intermediate stage of AMD. Therefore, the use of these supplements for patients who have less than intermediate AMD is not supported.[3]

**Intermediate AMD**

Daily doses of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80mg as zinc oxide), and copper (2 mg as cupric oxide, to reduce the risk of zinc-induced copper deficiency anemia) were evaluated in the original AREDS. Beta-carotene was replaced with lutein (10 mg) and zeaxanthin (2 mg) in AREDS2.

**TABLE 1. Antioxidant Vitamin and Mineral Supplements Used in the AREDS2[1]**

| 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<br>Data from 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;131:843-50 | |

The AREDS2 was a multicenter randomized double-masked placebo-controlled phase 3 study that used a 2 x 2 factorial study design. The population of the study represented a high-risk group for progression to more advanced stages as identified in the original AREDS. The final results of the AREDS2 support the substitution of beta-carotene with lutein (10mg) and zeaxanthin (2mg).[93-94]

In the original AREDS and in AREDS2, the patients who had either intermediate AMD or advanced AMD in one eye benefited from antioxidant vitamin and mineral supplementation. For patients with extensive intermediate/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. With this combination treatment, the risk of doubling the visual angle (i.e., losing vision of three or more lines) was reduced by 19%. 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 Original AREDS for Developing Advanced AMD and Vision Loss[1]**

| | 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 (three or more lines) | 19% | 11% | 10% |
| AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study | | | |

Data from the 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;119:1417-36.

A meta-analysis reported that there is an increased risk of adverse effects from nutritional supplementation. These include death from vitamin A, beta-carotene and vitamin E supplements (16%, 7% and 4% respectively) but not from vitamin C.[95] Concerns about this meta-analysis include a potential bias due to deletion of clinical trials with no deaths[96-97] and the use of antioxidant doses much higher than those used in AREDS.[98] Increased mortality among heavy smokers who were taking beta-carotene supplements to prevent lung cancer was reported.[95]

The AREDS2 study results demonstrated that the addition of omega-3 supplementation (DHA and EPA) had no further benefit on AMD progression.

Beta-carotene intake has been found to be associated with a higher incidence of lung cancer (not seen with lutein and zeaxanthin. Thus, beta-carotene was replaced by lutein and zeaxanthin in the supplement.[99-101]

**Xanthophyll Carotenoids: Lutein, Zeaxanthin and meso-Zeaxanthin**

Observational studies have shown that supplementation with the xanthophyll carotenoids namely: Lutein, Zeaxanthin and meso-Zeaxanthin increase macular pigment levels which improve visual function and reduce the risk of progression to late AMD especially neovascular AMD. Randomized, placebo-controlled clinical trials are ongoing to evaluate the preventive and therapeutic effects of lutein, zeaxanthin and meso-zeaxanthin on AMD as well as other eye diseases. [102]

**Neovascular AMD**

The VEGF inhibitors have been shown to improve visual and anatomic outcomes compared with other treatments. These agents have become the first-line treatment for treating and stabilizing most cases of neovascular AMD. The anti-VEGF inhibitor agents include: pegaptanib sodium (2004), off-label bevacizumab (2005), ranibizumab (2006) aflibercept (2012).

Intraocular injection of both Ranibizumab and aflibercept have been approved by the Food and Drug Administration (FDA) in both the USA and the Philippines for the treatment of all subtypes of neovascular AMD, based on results from double-masked randomized controlled trials. (see Table 3).

**TABLE 3. Anti-VEGF agents used in the treatment of neovascular AMD[1]**

| | **RANIBIZUMAB** | **AFLIBERCEPT** | **BEVACIZUMAB vs RANIBIZUMAB** |
|---|---|---|---|
| **Study** | MARINA [103] | VIEW 1 and 2 [104] | CATT [105] |
| **No. of patients** | 716 | 2419 | 1208 |
| **Patient Characteristics** | Mean age 77 years; BCVA 20/40 to 20/320; primary or recurrent CNV; | Mean age 76 years; BCVA 20/40 to 20/320; primary, active CNV | Mean age 79 years; BCVA 20/25 to to 20/320; untreated active CNV with CNV fluid or hemorrhage under the fovea |
| **Duration and Frequency of Treatment** | Monthly ranibizumab 0.5 mg injections for 2 years | 0.5 mg q 4 wks<br>0.2 mg q 4 wks<br>2.0 mg q 4 wks x 3 then q 8 wks<br><br>Ranibizumab 0.5 mg q 4 wks | Ranibizumab 0.5mg q 4wks<br>Bevacizumab 1.25mg q 4wks<br>Ranibizumab 0.5 mg PRN<br>Bevacizumab 1.25 mg PRN |
| **Treated Eyes** | | 4% | 4% Ranibizumab |

| | | | |
|---|---|---|---|
| Visual Loss of 15 letters or more*<br><br><br><br><br>Visual Gain of 15 Letters or more* | 10% (0.5 mg)<br><br><br><br><br>33% (0.5 mg) | 5%<br>4%<br><br>6% (ranibizumab)<br><br>30%<br>34%<br>31%<br><br>33% (ranibizumab) | 5% Bevacizumab<br>4% Ranibizumab<br>6% Bevacizumab<br><br><br>30% Ranibizumab<br>34% Bevacizumab<br>31% Ranibizumab<br>33% Bevacizumab |
| **Untreated Eyes**<br>Visual Loss of 15 letters or more*<br><br>Visual Gain of 15 Letters or more* | 47%<br><br><br>4% | NA<br>All patients received treatment | NA<br>All patients received treatment |
| **Years after Enrollment** | 2 | 1 | 1 |

Ranibizumab (0.5 mg) is a recombinant, humanized immunoglogulin antibody fragment developed specifically for intraocular use. Ranibizumab binds to and inhibits the biologic activity of all isoforms of human VEGF-A. The drug is approved by the FDA in the USA and the Philippines for intraocular injections.

Aflibercept (2 mg) is a pan-VEGF-A and placental growth factor (PGF) blocker that has been documented to be equivalent (i.e., noninferior) in efficacy to ranibizumab in the head-to-head phase III VEGF Trap-eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials.[104] The drug is approved by the USA and Philippine FDA for intraocular injections.

Bevacizumab (1.25 mg) is a full-length monoclonal antibody that binds all isoforms of VEGF. It is approved by the USA and Philippine FDA for intravenous use in the treatment of metastatic colorectal, metastatic breast and non-small cell lung cancer. Bevacizumab was first investigated as an intravenous treatment for AMD and later as an intravitreal injection (1.25 mg) before the US FDA approved ranibizumab.[106] Because initial reports of the use of bevacizumab as an intraocular injection were favorable, ophthalmologists began to use bevacizumab to treat CNV on an off-label basis.[107] Comparative trials and uncontrolled case series have reported improvements in visual acuity and decreased retinal thickening by OCT following intravitreal bevacizumab treatment.[108-115] Informed consent should be secured regarding the benefits and risks of intravitreal bevacizumab and its off-label status.

The Comparison of AMD Treatment Trials (CATT) was a multicenter clinical trial that compared the safety and effectiveness of bevacizumab to ranibizumab. It also compared pro re nata (PRN) or as-needed regimen to monthly injections. At 1 year, the CATT study found that ranibizumab and bevacizumab had comparable equivalence in visual acuity improvements following the monthly dosing schedule. [105] At 2 years of follow-up, the two drugs were comparable in both efficacy and safety but the PRN arms did not perform as well in terms of maintaining the visual gains at the end of 1 year.[105] Presently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab. There is likewise insufficient data to determine whether intravitreal anti-VEGF drugs significantly affect systemic safety.

The 5-year follow-up of patients in the CATT study confirms that anti-VEGF therapy is a major long-term therapeutic advancement for neovascular AMD. Although the vision gained in the first 2 years of the study were not maintained at 5 years, half of the eyes (647 patients) treated with either drug maintained 20/40 vision. 20% of the eyes declined to 20/200, which is thought to be an improved prognosis compared to the natural history of the disease. Between the 2$^{nd}$ to the 5$^{th}$ year in the CATT, the patients lost most of the improvement gained in the first two years. Among patients assigned to ranibizumab, 7.6% experienced arteriothrombotic events, compared with 4.5% to bevacizumab (P=0.04). The results highlight the need for pharmacologic advancements to prevent either the progression of geographic atrophy or an increase in the

size of the lesion. However, with most patients changing drugs over time, the ability to identify differential safety effects of the two drugs is compromised. Because very few patients continued to receive the originally assigned drug or dosing schedule between the end of year-2 and follow up at approximately 5 years, the CATT Follow-up Study results provide information primarily on over all treatment outcomes with anti VEGF drugs and limited information on effects of different drugs and dosing regimens.[116]

The Inhibit VEGF in Age-related Choroidal Neovacularization (IVAN) trial was a head to head comparison of ranibizumab and bevacizumab. The IVAN trial compared visual acuity and arteriothrombotic events between bevacizumab and ranibizumab in patients on a continuous and discontinuous treatment schedule for neovascular AMD. Patients received injections of either drug in the affected eye every month for the first three months. Patients were then subdivided to receive injections on a monthly basis or on an as-needed basis. The visual acuity at 2 years between the monthly and the PRN dosing schedules for ranibizumab and bevacizumab was equivalent, with slightly better results in patients treated on a monthly basis. However, geographic atrophy developed in a higher proportion of patients who received the monthly injections. Serious adverse events were similar for the two drugs. Fewer patients receiving bevacizumab experienced an arteriothrombotic event or heart failure. There was no difference between the drugs in the proportion experiencing serious systemic adverse events.[117-119]

LUCAS trial "Lucentis Compared to Avastin Study" 2016:[120] was a head to head, prospective, randomized, double-blind, multicenter, non-inferiority trial for 1 year that compared Ranibizumab and Bevacizumab. 432 patients with previously untreated CNVM and edema at the fovea were included. The study reported that Bevacizumab is non-inferior to Ranibizumab after 1 year on a treat-and-extend schedule in terms of vision gained and OCT measurements of the central fovea. The difference in mean VA at 1 year was 0.25 (P=0.850). The difference in mean macular thickness after 1 year was 10.5 um (P=0.340). The mean number of treatments in 1 year was 8 for ranibizumab and 8.8 for Bevacizumab (P=0.002). Serious systemic events at 1 year were likewise similar. Similar to the CATT, IVAN, MANTA, GEFAL and BRAMD trials, the LUCAS trial found that bevacizumab is non-inferior to ranibizumab in terms of vision gained and foveal measurement.

Dexamethasone intravitreal (DXI) implant that is injected into the vitreous remains an option as adjunctive therapy for patients with neovascular age-related macular degeneration. The most common adverse events include the development of cataracts and elevated intraocular pressure (IOP). Studies are ongoing to evaluate visual and anatomical benefits when treating with DXI as adjunct to an anti-VEGF medication.[121-122]

As anti-VEGF therapy has become the first line treatment for exudative AMD, photodynamic therapy (PDT) is used less frequently. However there remain select indications for PDT, including patients not candidates for and those refractory to anti-VEGF therapy. The role of combination treatments is not yet established but PDT, focal thermal laser photocoagulation, and radiotherapy continue to be investigated. Results suggest improved efficacy, reduced frequency of re-treatments, and reduced toxicity.

## CARE PROCESS

### DIAGNOSIS

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

**History**

An initial history should include the following:

- Symptoms [123]
    - Metamorphopsia
    - Decreased vision
    - Scotoma
    - Photopsia
    - Difficulties in dark adaptation
- Medication and nutritional supplements
- Ocular history [123-124]
- Medical history[123-124] (including any allergic reactions)
- Family history including history of AMD [50,125]
- Social history, especially smoking history [12-16]

**Physical Examination**

- Comprehensive eye examination
- Slit lamp/biomicroscopic stereoscopic examination of the macula

**Diagnostic Tests**

***Optical Coherence Tomography***

Determining the presence of subretinal fluid and documenting the degree of retinal thickening is important in the assessment of patients with neovascular AMD. This is done through optical coherence tomography of the macula, which defines the cross-sectional layers of the retina.[126] The scans can reveal subretinal fluid and retinal thickening that is not noted by biomicroscopy. It also helps in assessing the response of the retina, RPE and choroid to treatment because the structural changes can be monitored. [108-111] Spectral domain (SD) OCT is the newer generation of OCT and is the preferred technology at this time.[112-115] The ability of the SD-OCT in assessing the structure of the deeper layers of the choroid is much improved and enhanced by depth imaging.[114-115]

***Fluorescein Angiography***

Intravenous fluorescein angiography is indicated when the patient complains of new symptoms such as metamorphopsia, unexplained blurring of vision, and if the clinical eye exam shows elevation of the RPE or retina, macular edema, subretinal blood, hard exudates or subretinal fibrosis.[127]

The role and indications for fluorescein angiography are evolving as continued advances in OCT occur.

At this time, other indications to subject the patient to fluorescein angiography include the following objectives.

- To detect the presence and determine the extent, type, size and location of the CNV. If verteporfin PDT or laser photocoagulation is being considered, the angiogram is used as a guide to direct treatment.
- To detect persistent or recurrent CNV or retinal diseases following treatment (See Glossary)
- To assist in determining the cause of visual loss that is not explained by the clinical examination.

If the patient develops new symptoms or ocular findings, and if CNV is suspected, fluorescein angiography should be performed and interpreted expeditiously by an individual experienced in managing patients with neovascular AMD.[127]

Fluorescein angiography confers potential risks to the patient. The physician requesting this procedure must be aware of the unwanted complication that include: tissue infiltration from drug extravasation, allergic reactions, and even death from anaphylaxis (approximately 1 in 200,000). Every facility that performs this procedure must have a care plan in place in the event of an emergency situation. A clear protocol to minimize the risks and to manage complications should likewise be in place.

***Fundus Photography***

Color fundus photographs are also taken when fluorescein angiography is performed. Fundus photos are helpful in finding landmarks, evaluating serous detachments of the neurosensory retina and RPE and determining the etiology of blocked fluorescence. The fundus photos may also be used as baseline reference, for follow-up of treated eyes, and as tools to explain the pathology to the patient.

***Indocyanine Green Angiography***

Indocyanine green (ICG) angiography allows visualization of the choroidal circulation. For evaluating and treating AMD, the value of this test is debated.[128] The technique is useful in evaluating other forms of AMD, such as pigment epithelial detachments (PED), poorly defined CNV, occult CNV, retinal angiomatous proliferation and idiopathic polypoidal choroidal vasculopathy.[87,128-129] When ICG is performed, the requesting ophthalmologist must be aware of its potential risks including severe medical complications, allergic reactions and even death.

***Fundus Autofluorescence***

Fundus autofluorescence imaging has become increasingly valuable in documenting atrophic changes. It is helpful in demonstrating and monitoring the extent of drusen, pigment, areas of geographic atrophy and RPE damage or dysfunction as well as quantifying lipofuscin in the RPE.

***Other tests***

Other available tests to evaluate patients with AMD include microperimetery, optical coherence tomography (OCT) angiography and adaptive optics.

## MANAGEMENT

The aim of management is to arrest the deterioration in vision in order to help preserve each patient's quality of life and independence. This is best achieved by early detection and treatment. Management options for AMD include observation, antioxidant vitamin and mineral supplements, intravitreal injection of anti-VEGF agents, PDT and laser photocoagulation surgery.

Cigarette smoking should be stopped.[130] The physician's advice to stop smoking has been shown to be a helpful motivator for patients who wish to quit.[130] Long-term smoking abstinence has also been associated with a physician's advice.[131]

**Early Detection**

In patients with early AMD and or a family history of AMD, self-assessment or self-monitoring of monocular visual acuity with an Amsler grid is encouraged. Scheduled dilated eye examinations should also be adhered to in order to detect the intermediate stage of AMD. Treatment with antioxidant vitamins and minerals as

described in the original AREDS and AREDS2 trials is recommended in patients who have progressed to intermediate or advance AMD in at least one eye.

Patients should be advised about methods to detect new symptoms of CNV. This is particularly applicable in patients with high-risk AMD since they are at increased risk of progression to advanced AMD. Patients should also be educated about the importance of prompt consultation for new symptoms. The ophthalmologist can confirm if new symptoms are from CNV and if treatment is necessary.

Follow-up examinations at regular intervals are emphasized in patients who are at increased risk of progression to advanced AMD. This will enable:

- Early detection of asymptomatic and treatable CNV lesions that could improve vision
- Education about preventive regimens and the use of nutritional supplements (AREDS2)
- Reinforcement of the need for self-monitoring and prompt evaluation with the onset of new symptoms.

Patients who do self-monitoring or those who check their monocular near vision (reading/Amsler grid/Amsler grid equivalent) may be more likely to become aware of subtle visual symptoms due to CNV. This increases the likelihood of early detection of CNV at an early stage, which leads to better long-term visual outcomes with early treatment. Patients with unilateral disease are encouraged to monitor their vision in their fellow eye and to return periodically even in the absence of symptoms, but promptly after onset of new or significant visual symptoms.

Electronic monitoring devices are now available to aid in the detection of neovascular growth at an early stage. These devices include hyperacuity perimetry (or vernier acuity) to create a quantified central visual map of metamorphopsia or distorted vision.[132]

**Indications for Treatment of CNV**

Table 4 presents the assessment and treatment plans for non-neovascular and neovascular AMD.

**TABLE 4. Treatment Recommendations and Follow-up for AMD[1]**

| Recommended Treatment | Diagnoses Eligible for Treatment | Follow-up Recommendations | |
|---|---|---|---|
| | | Intervals | Testing |
| **Non-neovascular AMD** | | | |
| Observation with no medical or surgical therapies | 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, or OCT as appropriate |
| | Advanced AMD with bilateral subfoveal geographic atrophy or disciform scars | Return examination at 6-24 months if asymptomatic or prompt examination for new symptoms Fundus photos, fluorescein angiography, or as appropriate suggestive of CNV | Fundus photos, fluorescein angiography, or as appropriate |
| **Non-Neovascular AMD** | | | |

| | | | |
|---|---|---|---|
| Antioxidant vitamin and mineral supplements as recommended in the original AREDS and AREDS2 reports[3] | • Intermediate AMD (AREDS category 3)<br>•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)<br><br>•Fundus photography and/or fundus autofluorescence as appropriate<br><br>•Fluorescein angiography and/or OCT for suspicion of CNV |
| **Neovascular AMD**<br>Aflibercept intravitreal injection 2.0 mg as described in published reports[107] | 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<br><br>• 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.<br><br>• Monitoring of monocular near vision (reading/Amsler grid) | |
| Bevacizumab intravitreal injection 1.25 mg as described in published reports [105, 133-134]<br>The ophthalmologist should provide appropriate informed consent with respect to the off-label status | 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.<br><br>• Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist<br><br>• Monitoring of monocular near vision (reading/Amsler grid) | |
| Ranibizumab intravitreal injection 0.5 mg as recommended in literature [100, | 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<br><br>• Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist<br><br>• Monitoring of monocular near vision (reading/Amsler grid) | |
| **Less Commonly Used Treatments for Neovascular AMD**<br>PDT with verteporfin as recommended in the TAP[139] and VIP[140] reports* | • 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<br><br>• Occult CNV may be considered for PDT with vision <20/50 or if the CNV is <4 MPS disc areas in size | • Return examination approximately every 3 months until stable, with retreatments as indicated<br><br>• Monitoring of monocular near vision (reading/Amsler grid) | |

| | | |
|---|---|---|
| | when the vision is >20/50<br><br>•Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases | |
| Thermal laser photocoagulation surgery as recommended in the MPS reports[127] | • May be considered for extrafoveal classic CNV, new or recurrent<br><br>• 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 finding<br><br>• Retreatments as indicated<br><br>• 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; 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.

Treatment trials as a general rule, do not describe clear guidance for the management of patients.

The major prospective randomized anti-VEGF treatment trials include:

- Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV (ANCHOR)
- Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA)
- VIEW
- CATT
- IVAN
- HARBOR

These studies used either a fixed continuous treatment intravitreal injection regimen of approximately 4-8 weeks or an individualized discontinuous, "as-needed" PRN treatment schedule.

The PRN treatment regimens with ranibizumab and aflibercept have been shown to have comparable efficacy and safety to fixed continuous regimens over 1 year of treatment. The PRN regimen however, does not maintain the initial visual gains with longer follow-up.

A PRN regimen for bevacizumab has been shown to be less effective than when used on a monthly basis.

A continuous, variable dosing regimen that attempts to individualize therapy, called the "treat and extend" (TER) schedule is frequently used in clinical practice as an alternative to the monthly or PRN dosing. Studies using this "treat and extend" regimen have been described in smaller uncontrolled trials.[134-136]

**PRN vs Treat-and-Extend Regimen (TER)**[141]

Current evidence favors pro-activity with a TER approach rather than risking the negative effects associated with under-treatment in PRN regimen.

Recommendations:

Monthly injections should continue until the following (maximum response) is observed:

1) complete resolution of subretinal fluid (SRF) and intraretinal fluid (IRF) without new retinal hemorrhage
2) no further reduction of SRF or IRF on OCT for at least 2 consecutive visits in the absence of new retinal hemorrhage.
3) no further flattening of serous or vascularized pigment epithelial detachments
4) no further improvement in visual acuity, in their definition of maximal response.

Once maximal response is achieved, treatment intervals can be extended 2 weeks at a time, if there is either no new hemorrhage or a continued absence (preferred) or stabilization of intraretinal or subretinal fluid for at least two consecutive injections assessed by OCT. Visual changes should be evaluated in the context of the clinical examination and OCT findings. The injection interval should be shortened by 1-2 weeks for minor changes. Re-induction of monthly treatments should be considered if more severe deterioration occurs. [142]

Neovascular AMD commonly presents with subretinal hemorrhage. This finding is a sign of active CNV or of polypoidal choroidal vasculopathy and may be managed with anti-VEGF therapy. For the management of larger submacular hemorrhages, pneumatic displacement procedures, the use of tissue plasminogen activator (tPA) and/or pars plana victrectomy have been proposed and continue to be under study.

The risks, benefits, complications and alternatives of the treatment should be discussed with the patient and informed consent obtained. Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breast-feeding, or of pediatric age.

**Complications of Treatment**

The possible unwanted complications of the four main methods of treatment for AMD are discussed below.

Retinal pigment epithelial rips (tears) may occur with or without performing the treatment methods. RPE rips are not a contraindication to continued anti-VEGF therapy.

***Intravitreal Pharmacotherapy***

All anti-VEGF treatments may carry theoretical risks for systemic arterial or venous thromboembolic events and increased intraocular pressure, although the results of clinical trials studying these risks remain inconclusive. [143]

The risks of intravitreal anti-VEGF agents in pregnant or lactating women have not been studied. [144-145]

The potential ocular complications are listed below.

- Cataract
- Endophthalmitis
- Increase in intraocular pressure (IOP)
- Rhegmatogenous retinal detachment
- Subconjunctival hemorrhage (the most common)
- Tractional retinal detachments
- Uveitis
- Vitreous Hemorrhage

The potential systemic complications are listed below.

- Arteriothrombotic events
- Venous thrombotic events
- Gastrointestinal disorders such as hemorrhage

The CATT study had limited statistical power to identify any differences in treatment-related adverse events between ranibizumab and bevacizumab. 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 difference was persistent at 2 years of follow-up.[105] The IVAN trial showed greater serum VEGF suppression with bevacizumab but did not show any statistically significant difference in serious systemic adverse events. [133-134]

***Photodynamic Therapy***

The most common adverse reactions associated with PDT include visual disturbances and infusion site reactions. A small percentage of patients report sudden decrease in vision following treatment. Less commonly reported events include infusion related back pain and vitreous hemorrhage. Photosensitivity reactions have been reported as well, characterized as a sunburn usually occurring within 24 hours of verteporphin infusion. Hence, patients are typically advised to use protective clothing and avoid sun exposure when possible. Rarely reported events include choroidal non-perfusion and RPE tears.

***Thermal Laser Photocoagulation Surgery***

The possible complications of laser photocoagulation for AMD are listed below.

- Severe vision loss which may be permanent
- Vitreous or subretinal hemorrhage from rupture of Bruch's membrane
- Effects on the fovea from RPE pigmentation changes

The formation of a scotoma or the enlargement of an existing scotoma with or without visual acuity loss is not a complication of thermal laser treatment. It is an anticipated side effect of the treatment. Likewise, in patients who have received adequate laser treatment, the recurrence or persistence of CNV or the development of a new CNV and further visual deterioration is usually a result of the disease process and is not a complication. The patient and the family must be informed about these realities before treatment.

***Supplements of High-Dose Antioxidants and Zinc***

- Beta-carotene
    - Increased yellowing of the skin (8.3% compared with 0.6%, *P*=0.008)[3]
    - Increased risk of developing lung cancer in current smokers or former smokers who stopped within the last year [100-101]
- Zinc
    - Increased risk of hospitalizations for genitourinary causes (7.5% in those treated with zinc compared with 4.9% in those not treated wit 80 mg zinc, *P=0.0001)* [3] In AREDS2, there was no significant difference in AMD progression between 80 mg and 25 mg zinc
    - Copper deficiency anemia (concomitant administration of copper is necessary)

The high doses of anti-oxidant vitamins and mineral supplementation recommended by the original AREDS and AREDS2 have been reported to be associated with an increased rate of genitourinary conditions. Thus co-management with the patient's primary care physician is suggested.

**Follow-up Evaluation**

A history and examination are the essential elements of the follow-up visits.

***History***

The patient should be interviewed about the following in the follow-up visit:

- Symptoms, including decreased vision and metamorphopsia
- Changes in medications and nutritional supplements
- Changes in medical and ocular history
- Changes in social history (smoking)

***Examination***

The follow-up visit examinations should evaluate the following:

- Visual acuity
- Stereoscopic biomicroscopic examination of the fundus

***Follow-up after Treatment for Neovascular AMD***

In addition to the above elements of the history and examination, patients who have been treated for AMD with aflibercept, bevacizumab, ranibizumab, or pegaptanib sodium injection, verteprofin PDT or thermal laser photocoagulation surgery should be evaluated at regular intervals with OCT, FA and fundus photography when indicated. These exams may be helpful to detect signs of active exudation or disease progression. OCT is a non-invasive procedure that is well accepted by the patient and provides important information for the physician in the management of AMD.

The initial treatment and follow-up evaluation in patients treated with anti-VEGF (aflibercept, bevacizumab, ranibizumab) should be at approximately 4 weeks. The interval for subsequent follow-up visits vary depending on the clinical findings and the judgment of the treating ophthalmologist.

An every 8 week treatment regimen with aflibercept has been shown to have comparable efficacy to every 4 weeks of either ranibizumab and aflibercept in the first year of therapy. [104]

There is no consensus about the ideal treatment intervals with anti-VEGF agents. At this time, there are three protocols: (1) monthly or bi-monthly, (2) treat-and-extend or (3) PRN. The treat-and-extend regimen (TER) is a schedule of anti-VEGF treatment based on the treatment response. As-needed or PRN treatment is based on the presence or absence of subretinal or intraretinal fluid.

Repeat examinations with OCT and fluorescein angiography are performed based on the judgment of the treating ophthalmologist and the clinical findings on follow up examination of the patient. Treated patients should be taught to consult promptly if symptoms related to endophthalmitis, retinal detachment or decreased vision occur.

## PROVIDER AND SETTING

Clinical personnel should be made aware that patients consulting for new symptoms suggestive of AMD (e.g., visual loss, metamorphopsia, or scotoma) should be examined promptly. Data collection and other aspects of the examination may be conducted by other trained individuals under supervision by the ophthamologist. Most of the eye examination; however, should be performed by the treating ophthalmologist.

The VitreoRetina Society of the Philippines (VRSP) has made a consensus statement regarding the role of the ophthalmologist in the delivery of intravitreal agents. (See Appendix 3)

## COUNSELING AND REFERRAL

All patients with AMD should be educated about the prognosis of the disease and the potential value of treatment that is appropriate for their visual and functional status. Patients should be educated that complete visual loss is not common, but central vision loss is. Patients may continue to use their eyes for daily tasks. Moreover, the effect of total sunlight exposure on the progression or development of AMD is not proven. Cigarette smoking; however, is a key modifiable risk factor and smoking cessation is strongly recommended.

All patients receiving treatment should go through the informed consent process. This includes a discussion on the risks and benefits of treatment and treatment alternatives. The discussion about bevacizumab should include its off-label status.

Functional ability can be assisted by vision rehabilitation.[146] Patients with reduced visual function should be advised about vision rehabilitation and social services.[147] Patients should be educated that the vision rehabilitation specialist will help them to optimize their existing visual function and will most likely not be able to help them to see better. Special optical or electronic magnifying lenses, bright lights and electronic reading aids may help patients to read better but not to the same level before the onset of AMD.

The risk of frequent falls increases when central vision is lost.[148-149] Depression and visual hallucinations (Charles Bonnet syndrome) may occur with severe central vision loss. Patients and their families should be counseled regarding the unusual visual symptoms that may occur with the Charles Bonnet syndrome. These are not signs of psychosis or mental deterioration.

## SOCIOECONOMIC CONSIDERATIONS

The use of anti-VEGF in the treatment of AMD has been shown to be highly cost-effective when compared to prior therapies such as photodynamic therapy.[150-152] The off-label use of intravitreal bevacizumab has been suggested to be a highly cost-effective, off-label option when compared to the more costly drugs: ranibizumab and aflibercept.[151]

The CATT trial found that bevacizumab could be of greater value when compared to ranibizumab in the treatment of neovascular AMD among patients 80 and older.[151-155]

Physicians should avoid financial conflicts of interest in their decisions regarding treatment options.

# APPENDIX 1. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades reported here have been adapted from the AAO PPP on Diabetic Retinopathy 2016.

Details of these grading systems are reported in the Methods and Key to Ratings presented below.

**Methods and Key to Ratings**

Preferred Practice patterns® 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[156] (SIGN) (I++; I+;I-;II++,II+; II-; III) and the Grading of Recommendations Assessment, Development and Evaluation[157] (GRADE) . GRADE is a systematic approach to grading the strength of the total body of evidence (Good, Moderate, Insufficient) that is available to support recommendations on a specific clinical management issue (Strong, Discretionary). Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency or Healthcare Research and Policy, and the American College of Physicians.[158]

- 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[156] 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<br>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 | Non-analytic studies (e.g. case reports, case series) |

- Recommendations for care are formed based on the body of evidence. The body of evidence quality ratings are defined by GRADE[157] 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 unlikely to have an important impact on our confidence in the estimate of effect is likely to change the estimate<br><br>Any estimate of effect is very uncertain |

- Key recommendations for care are defined by GRADE[157] 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, adapted from the AAO, were rated using the system described above.

**Highlighted Findings and Recommendations for Care[1]**

- Page 3: Antioxidant vitamin and mineral supplementation as per the original AREDS and AREDS2 trials should be considered in patients with intermediate or advanced age-related macular degeneration (AMD): I++; Good; Discretionary
- Page 3: Intravitreal injection therapy using pan-vascular endothelial growth factor (VEGF) inhibiting agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD, and it represents the first line of treatment: I++; Good; Strong
- Page 3: Symptoms suggestive of post-injection endophthalmitis or retinal detachment require prompt evaluation: III; Good; Strong

**Risk Factors[1]**

- Page 5: Smoking cessation is strongly recommended when advising patients: I++; Good; Strong

**Natural History[1]**

- Page 7: Reticular pseudodrusen are best imaged using fundus autofluorescence, infrared reflectance, and/or spectral domain optical coherence tomography (SD-OCT) imaging: III; Moderate; Discretionary

**Treatment Modalities[1]**

- Page 9: There is no evidence to support the use of antioxidant vitamin and mineral supplements for patients who have less than intermediate AMD: I++; Good; Discretionary
- Page 10: Anti-VEGF therapies have become first-line therapy for treatment and stabilizing cases of neovascular AMD: I++; Good; Strong

**Care Process[1]**

- Page 13: 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: II++; Good; Strong
- Page 13: An initial history should consider symptoms of metamorphopsia, decreased vision, scotoma, photopsia: II-; Good; Strong

- Page 13: An initial history should consider medication and nutritional supplement use: III; Good; Strong
- Page 13: An initial history should consider ocular history: II+; Good; Strong
- Page 13: An initial history should consider medical history: II+; Good; Strong
- Page 13: An initial history should consider family history: II+; Good; Strong
- Page 13: An initial history should consider social history: III; Good: Strong
- Page 13: A physical examination should include a comprehensive eye exam: II++; Good; Strong
- Page 13: A physical examination should include stereoscopic biomicroscopic examination of the macula: III; Good; Strong
- Page 13: Binocular slit-lamp biomicroscopy of the ocular fundus is often necessary to detect subtle clinical signs of CNV: III; Good; Strong
- Page 13: OCT is important in diagnosing and managing AMD, particularly with respect to determining the presence of subretinal fluid and in documenting the degree of retinal thickening: III; Good; Strong
- Page 13: OCT also assists in evaluating the response of the retina and RPE to therapy by allowing structural changes to be followed accurately: II+; Good; Strong
- Page 13: Newer-generation OCT modalities, including spectral domain OCT, are preferred technologies: III; Insufficient; Discretionary
- Page 13: Intravenous fundus fluorescein angiography is indicated 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: II-; Good; Strong
- Page 14: Intravenous fundus fluorescein angiography is helpful to detect the presence of and determine the extent, type, size and location of CNV: III; Insufficient; Discretionary
- Page 14: Intravenous fundus fluorescein angiography is helpful to detect persistent or recurrent CNV or other retinal diseases following treatment: III; Insufficient; Discretionary
- Page 14: Intravenous fundus fluorescein angiography is helpful to assist in determining the cause of visual loss that is not explained by the clinical examination: III; Insufficient; Discretionary
- Page 14: If CNV is suspected on the basis of new symptoms or ocular findings, fluorescein angiography [and/or optical coherence tomography] should be performed and interpreted expeditiously by an individual experienced in managing patients with neovascular AMD: III; Good; Strong
- Page 14: If fluorescein angiography is performed, the physician must be aware of potential risks associated with this procedure: II-; Good; Strong
- Page 14: 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: III; Good; Strong
- Page 14: 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: III; Good; Discretionary
- Page 14: 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: III; Good; Discretionary
- Page 14: Indocyanine green angiography has been shown to be useful in evaluating specific forms of AMD, such as pigment epithelial detachment, poorly defined CNV, occult CNV, and lesions including retinal angiomatous proliferation or idiopathic polypoidal choroidal vasculopathy: II-; Moderate; Discretionary
- Page 14: 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: III; Good; Strong
- Page 14: Several other tests including fundus autofluorescence, microperimetry and adaptive optics have been used for evaluation of patients with AMD; however, their role in clinical practice is poorly defined at this time: III; Insufficient; Discretionary
- Page 14: Patients who are currently smoking should be advised to stop: I++; Good; Strong

- Page 15: Patients with early AMD and/or a family history of AMD should be encouraged to assess their own visual acuity using monocular vision testing (i.e., Amsler grid), and have scheduled dilated eye examinations for detecting the intermediate stage of AMD: III; Good; Strong
- Page 15: Treatment with antioxidants and minerals as described previously in the original AREDS and AREDS2 trials is recommended for patients who have progressed to intermediate or advanced AMD in at least one eye: I++; Good; Strong
- Page 15: 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: III; Good; Strong
- Page 15: Instruct patients with unilateral disease to monitor their vision in their fellow eye and to return periodically even in absence of symptoms, but promptly after onset of new or significant visual symptoms *(III, GQ, SR)*
- Page 15: Patients with a high risk AMD phenotype should 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: III; Good; Strong
- Page 15: Electronic monitoring devices are now available to aid in the detection of neovascularization at an early stage: I+; Good; Discretionary
- Page 15: The major anti-VEGF trials have used either a fixed, continuous treatment regimen (approximately every 4 to 8 weeks) or an individualized, discontinuous treatment regimen (PRN): I++; Good; Discretionary
- Page 15: Table 4, Non-Neovascular AMD, Observation, Early AMD, Intervals: Return examination at 6–24 months if asymptomatic or prompt examination for new symptoms suggestive of CNV: III; Good; Discretionary
- Page 15: Table 4, Non-Neovascular AMD, Observation, Early AMD, Testing: Fundus photos, fluorescein angiography, or OCT as appropriate: III; Good; Strong
- Page 15: Table 4, Non-Neovascular AMD, Observation, Advanced AMD, Intervals: Return examination at 6–24 months if asymptomatic or prompt examination for new symptoms suggestive of CNV: III; Good; Discretionary
- Page 15: Table 4, Non-Neovascular AMD, Observation, Advanced AMD, Testing: Fundus photos, fluorescein angiography, or as appropriate: III; Good; Strong
- Page 16: Table 4, Non-Neovascular AMD, AREDS Supplements, Intervals: Return examination at 6–18 months if asymptomatic or prompt examination for new symptoms suggestive of CNV: III; Good; Discretionary
- Page 16: Table 4, Non-Neovascular AMD, AREDS Supplements, Testing: Monitoring of monocular near vision (reading/Amsler grid): III; Good; Strong
- Page 16: Table 4, Non-Neovascular AMD, AREDS Supplements, Testing: Fundus photography and/or fundus autofluorescence as appropriate: III; Good; Strong
- Page 16: Table 4, Non-Neovascular AMD, AREDS Supplements, Testing: Fluorescein angiography and/or OCT for suspicion of CNV: III; Good; Strong
- Page 16: Table 4, Neovascular AMD, Aflibercept: 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: III; Good; Strong
- Page 16: Table 4, Neovascular AMD, Aflibercept: Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist. An every 8-week maintenance treatment regimen has been shown to have comparable results to every 4 weeks in the first year of therapy: III; Good; Discretionary
- Page 16: Table 4, Neovascular AMD, Aflibercept: Monitoring of monocular near vision (reading/Amsler grid): III; Good; Strong
- Page 16: Table 4, Neovascular AMD, Bevacizumab: The ophthalmologist should provide appropriate informed consent with respect to the off-label status: III; Good; Strong

- Page 16: Table 4, Neovascular AMD, Bevacizumab: 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: III; Good; Strong
- Page 16: Table 4, Neovascular AMD, Bevacizumab: Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist: III; Good; Discretionary
- Page 16: Table 4, Neovascular AMD, Bevacizumab: Monitoring of monocular near vision (reading/Amsler grid): III; Good; Strong
- Page 16: Table 4, Neovascular AMD, Ranibizumab: 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: III; Good; Strong
- Page 16: Table 4, Neovascular AMD, Ranibizumab: Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist: III; Good; Discretionary
- Page 16: Table 4, Neovascular AMD, Ranibizumab: Monitoring of monocular near vision (reading/Amsler grid): III; Good; Strong
- Page 16: Table 4, Verteporfin: Return examination approximately every 3 months until stable, with retreatments as indicated: III; Good; Discretionary
- Page 16: Table 4, Verteporfin: Monitoring of monocular near vision (reading/Amsler grid): III; Good; Strong
- Page 17: Table 4, Thermal laser: 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: III; Good; Discretionary
- Page 17: Table 4, Thermal laser: Retreatments as indicated: III; Good; Discretionary
- Page 17: Table 4, Thermal laser: Monitoring of monocular near vision (reading/Amsler grid): III; Good; Strong
- Page 17: Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens: I++; Moderate; Discretionary
- Page 17: A continuous, variable dosing regimen that attempts to individualize therapy and is commonly referred to as “treat and extend” is frequently used in clinical practice as an alternative to the two treatment approaches above: III; Insufficient; Discretionary
- Page 18: The risks, benefits, complications, and alternatives of the treatment should be discussed with the patient and informed consent obtained: III; Good; Strong
- Page 18: Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breast-feeding, or of pediatric age: III; Good; Strong
- Page 19: Introduction or enlargement of a pre-existing scotoma, with or without visual acuity loss, is not a complication of thermal laser photocoagulation; 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: III; Good; Strong
- Page 19: 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: III; Good; Strong
- Page 19: A history and examination are the recommended elements of the follow-up visits: III; Good; Strong
- Page 19: The follow-up history should take into account symptoms, including decreased vision and metamorphopsia: II-; Good; Strong
- Page 19: The follow-up history should take into account changes in medications and nutritional

supplements: III; Good; Strong

- Page 19: The follow-up history should take into account changes in medical and ocular history: II+; Good; Strong
- Page 20: The follow-up history should take into account changes in social history (smoking): III; Good; Strong
- Page 20: The examination on the follow-up visit should include visual acuity: III; Good; Strong
- Page 20: The examination on the follow-up visit should include stereoscopic biomicroscopic examination of the fundus: III; Good; Strong
- Page 20: 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: III; Good; Strong
- Page 20: OCT, fluorescein angiography,and fundus photography may be helpful to detect signs of active exudation or disease progression and should be used when clinically indicated: III; Insufficient; Discretionary
- Page 20: Initial treatment and follow-up with intravitreal anti-VEGF therapy (aflibercept, bevacizumab and ranibizumab) should be at approximately 4 weeks: III; Good; Strong
- Page 20: Subsequent follow-up and treatment intervals vary depending on the clinical findings and judgment of the treating ophthalmologist: I++; Moderate; Discretionary
- Page 20: Subsequent examinations, OCT, and fluorescein angiography should be performed as indicated depending on the clinical findings and the judgment of the treating ophthalmologist: III; Good; Discretionary
- Page 20: Treated patients should be instructed to report symptoms of endophthalmitis, retinal detachment, or decreased vision, and should be re-examined promptly: III; Good; Strong
- Page 20: 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: III; Good; Strong
- Page 20: Instruct patients to 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 promptly *(III, GQ, SR)*
- Page 20: 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: III; Good; Strong
- Page 20: 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: III; Good; Strong
- Page 20: 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: III; Good; Discretionary
- Page 21: 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 educated 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: III; Good; Strong
- Page 21: 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: III; Good; Strong
- Page 21: Vision rehabilitation restores functional ability and patients with reduced visual function should be referred for vision rehabilitation and social service: III; Good; Strong
- Page 21: 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: III; Insufficient; Discretionary
- Page 21: Patients with 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: III; Good; Strong

- Page 21: 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: III; Good; Strong

## APPENDIX 2: Consensus on Intravitreal Injection Technique*: VitreoRetina Society of the Philippines

***The consensus pertains to injections in adults only. It does not encompass injections for Retinopathy of Prematurity (ROP) in neonates and children**

Vascular endothelial growth factor (VEGF) has been shown to play a central role in the pathophysiologic process underlying neovascular eye diseases. As such, anti-VEGF based pharmacologic agents have emerged as a highly effective treatment modality for various visually debilitating retinal and choroidal vascular pathologies. The introduction of these pharmacologic agents directly into the vitreous cavity by means of an injection through the pars plana has become a widely performed ophthalmic procedure both locally and overseas.

As the sole physician organization of vitreoretinal specialists in the country, the VitreoRetina Society of the Philippines (VRSP), in coordination with the Philippine Academy of Ophthalmology (PAO), through a review of current evidence and a consensus among its members has developed guidelines for the performance of intravitreal injections in the Philippine setting to ensure patient safety and to maximize the benefits Filipino patients may obtain from this highly valuable treatment modality.

I. All intravitreal injections should be performed by a Philippine Board of Ophthalmology certified ophthalmologist who is knowledgeable, skilled and comfortable in the diagnosis and comprehensive management of retinal diseases for which anti-VEGF treatment is indicated, and adept at minimizing the risks and managing the potential complications associated with trans pars plana delivery of these medications.

II. Clinical Setting of Care:
- It is suggested that the procedure be performed in an operating theater or in a room/facility specifically dedicated for intravitreal injections.[1,2]

III. Preprocedural Issues
- Informed Consent [3]
    i. An informed consent has to be signed by the patient prior to the procedure.
    ii. The consent form should include the name of the drug to be injected, the indication for injection, the potential risks and benefits of the use of anti-VEGF agents and of the procedure itself.
    iii. Information must be fully explained to the patient.
    iv. A consent form specific for an individual drug is recommended.

- Currently, there is no data that indicates anticoagulant use will affect visual outcomes after intravitreal injection. However, there is an increased likelihood of subconjunctival hemorrhage at the site of injection.
- Medical Clearance
    i. The benefits, risks and indications of anti-VEGF injections should be carefully reconsidered in the following situations:
        1. Patients with a history of myocardial infarction, any cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within the past 4 months [4]
        2. Major surgery within 28 days
        3. Uncontrolled hypertension
        4. Pregnancy
    ii. Necessity for medical clearance is at the discretion of the attending ophthalmologist. While arteriothromboembolic events have been reported, the direct causative relation between stroke and intravitreal anti-VEGF injection use has not been established.

IV. Surgical Site Preparation

- Intravitreal injections are intraocular procedures that merit equal attention to adherence to principles of asepsis and sterile technique as for conventional intraocular surgeries.
- As part of the World Health Organization Surgical Safety Checklist,[5] "time-out" or surgical site marking is recommended.
- Pre-operative dilation is performed at the discretion of the attending ophthalmologist
- There is no evidence to support that the instillation of a topical antibiotic solution prior to injection reduces the risk of subsequent intraocular infection. Pre-operative antibiotics may be administered at the discretion of the attending ophthalmologist.
- Preoperative disinfection of the *periocular skin* with 10% povidone iodine and a minimum exposure time of 3 minutes is suggested. 10% aqueous chlorhexidine may be used as an alternative in patients with hypersensitivity to povidone iodine. [6]
- The use of a newly opened bottle of topical anesthetic is recommended.
- 5% povidone iodine should be applied onto the *conjunctival cul-de-sac* or *lower fornix* with a minimum contact time of 30 seconds. [6,7,8,9,10,11]
- The use of a sterile solid-blade lid speculum[9, 10] or any type of occlusive dressing is recommended to isolate the lashes from the site of injection.

V. Injection Procedure

- As part of good surgical practice, the use of a sterile eye sheet or equivalent drapes,[11] the donning of sterile surgical gloves and the wearing of a surgical mask [11, 12] are advised. The surgical assist is advised to wear a surgical cap and mask.
- The injection site should be 3 to 3.5 mm from the corneoscleral limbus for aphakic and pseudophakic eyes, and 3.5 to 4 mm for phakic eyes.
- The use of a sterile 30-gauge needle is recommended for intravitreal injection of anti-VEGF drugs.
- Once the needle is withdrawn, the ophthalmologist may apply a sterile cotton applicator to prevent reflux of liquid vitreous.
- The ophthalmologist should assess central retinal artery perfusion by checking for gross vision *or* venous pulsation via indirect ophthalmoscopy.
- Anterior chamber paracentesis may be performed in cases with evidence of a sustained rise in intraocular pressure.
- Bilateral Same Day Injections [13]
    i. Each eye should be prepared with povidone-iodine separately.

ii. A completely new and different surgical set of sterile eye sheet, lid speculum, instruments, 30-gauge needle and syringe should be utilized.
iii. Whenever feasible, separate vials of medication with different lot numbers should be used for each eye.

- There is no evidence to suggest that the instillation of post-injection antibiotics confers additional benefit in reducing the risk of endophthalmitis following intravitreal injections. Post injection antibiotics may be administered at the discretion of the attending ophthalmologist.

VI. Post-Injection Management

- Post-injection follow-up is recommended within 7 days.
- Patient should be instructed to return sooner if with symptoms of inflammation or infection.

This consensus statement is subject to re-evaluation and revision as new evidence-based studies on intravitreal anti-VEGF injections become published and new practice patterns evolve.

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## GLOSSARY: as cited in AMD PPP - Updated 2015 AAO Retina/Vitreous PPP Panel, Hoskins Center for Quality Eye Care[1]

***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 mineral 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 (docosoahexaenoic 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. This condition is characterized by the presence of drusen and alterations of the RPE as well as 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: Amsler grid:*** This is a graph 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

***Bevacizumab (Avastin):*** Bevacizumab is 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 neovascularizatioin (CNV):*** Synonymous with “subretinal or choroidal neovascular membrane”. These are vessels of 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 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 mm (1500 um) equal to 1.77 square mm. The area of 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:*** 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 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 choroidal neovascularization.

***Inhibition of VEGF in Age-Related choroidal Neovascularization (IVAN):***

***IVAN trial:*** This study compared intravitreal bevacizumab to ranibizumab dosed either on a continuous (monthly) or discontinuous (PRN) basis. It was a 2-year study conducted in the United Kingdom.

***Juxtafoveal choroidal neovascularization:*** Well-demarcated CNV that is between 1 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.

***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.

***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.

***PAO:*** Philippine Academy of Ophthalmology

***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 non-thermal 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 serosanguinous RPE detachments, which often resemble hemorrhagic detachment in AMD. A fluorescein angiogram and indocyanine green 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.

***RAP:*** See Retinal angiomatous 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.

***Reticular pseudodrusen:*** Also referred to as subretinal drusenoid deposits.

***Retinal angiomatous 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.

***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.

***VRSP:*** VitreoRetina Society of the Philippines

## SUMMARY BENCHMARKS

**Treatment Recommendations and Follow-up Plans for Age-Related Macular Degeneration[1]**

| Recommended Treatment | Diagnoses Eligible for Treatment | Follow-up Recommendations |
|---|---|---|
| Observation with no medical or surgical therapies | No clinical signs of AMD (AREDS category 1) Early AMD<br><br>(AREDS category 2)<br><br>Advanced AMD with bilateral subfoveal geographic atrophy or disciform scars | As recommended in the Comprehensive Adult Medical Eye Evaluation PPP<br><br>Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV<br><br>OCT, fluorescein angiography, or fundus photos as appropriate<br><br>Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV<br><br>Fundus photos or fluorescein angiography as appropriate |
| Aflibercept intravitreal injection 2.0 mg as described in published reports | Macular CNV | 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<br><br>Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist. An every 8-week maintenance treatment regimen has been shown to have comparable results to every 4 weeks in the first year of therapy.<br><br>Monitoring of monocular near vision (reading/Amsler grid) |
| Bevacizumab intravitreal injection 1.25 mg as described in published reports The ophthalmologist should provide appropriate informed consent with respect to the off- label status | Macular CNV | Patients should be instructed to report any symptoms suggestive of endophthalmitis promptly, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters<br><br>Return exam approximately 4 weeks after treatment; subsequent follow-up depends on the clinical findings and judgment of the treating ophthalmologist<br><br>Monitoring of monocular near vision (reading/Amsler grid) |
| | | |
| Ranibizumab intravitreal injection 0.5 mg as recommended in ranibizumab literature | Macular CNV | Patients should be instructed to report any symptoms suggestive of endophthalmitis promptly, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters<br><br>Return exam approximately 4 weeks after treatment; subsequent follow-up depends on the clinical findings and judgment of the treating ophthalmologist |

| | | |
|---|---|---|
| | | Monitoring of monocular near vision (reading/Amsler grid) |
| PDT with verteporfin as recommended in the TAP and VIP reports | Macular CNV, new or recurrent, where the classic component is >50% of the lesion and the entire lesion is ⍰5400 microns in greatest linear diameter<br><br>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<br><br>Juxtafoveal CNV is an off-label indication for PDT, but may be considered in select cases. | Return exam approximately every 3 months until stable, with retreatments as indicated<br><br>Monitoring of monocular near vision (reading/Amsler grid) |
| Thermal laser photocoagulation surgery as recommended in the MPS reports | May be considered for extrafoveal classic CNV, new or recurrent<br>May be considered for juxtapapillary CNV | Return exam with fluorescein angiography approximately 2 to 4 weeks after treatment, and then at 4 to 6 weeks and thereafter depending on the clinical and angiographic findings<br>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; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy

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