Table 3. Main findings from 33 reliable systematic reviews and mapping to clinical practice guidelines

Author	Year	Main findings of the systematic review	American Academy of Ophthalmology (AAO) Preferred Practice Pattern (PPP) Guideline Statement (2015)
Anti-vascular endothelial growth factor (anti-VEGF) agents (n = 10)			
Takeda, et al[45]	2007	"Pegaptanib and ranibizumab appear to slow or stop the progression of neovascular AMD. Uncertainty remains over the relative benefits of pegaptanib compared with ranibizumab and other unlicensed drugs (eg, Avastin), due to the nature of the evidence. Head-to-head RCTs and economic evaluations comparing these alternatives are needed."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Colquitt, et al[62]	2008	"Patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or PDT. Patients who continued treatment with either drug appeared to maintain benefits after 2 years of follow-up. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Vedula, et al[30]	2008	"Pegaptanib and ranibizumab reduce the risk of visual acuity loss in patients with neovascular AMD. Ranibizumab causes gains in visual acuity in many eyes. Quality of life and cost will be important for treatment decisions. Other agents blocking VEGF are being tested in ongoing trials."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Schouten, et al[44]	2009	"Visual acuity improves and central retinal thickness decreases in patients with exudative AMD after bevacizumab. There is no reasonable doubt that this is caused by bevacizumab. It is likely that a randomized controlled trial will show that bevacizumab is equivalent in effect to ranibizumab, which showed a change in ETDRS of +5.9 letters for occult or minimally classic CNVand +9.8 letters for classic CNV after three monthly injections in two large RCTs."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Ziemssen, et al[47]	2009	"In 33 studies, there was consistent and clear evidence for the efficacy of bevacizumab in neovascular AMD."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Schmucker, et al[42]	2010	"Given the lack of controlled data, the widespread off-label use of bevacizumab is not justified in clinical practice. On the other hand, a major challenge in the management of patients who require repeated antivascular endothelial growth factor injections is the high cost of ranibizumab. This dilemma underlines the need for head-to-head studies comparing both vascular endothelial growth factor antibodies, or, at least, well conducted randomized controlled trials evaluating intravitreal bevacizumab."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Jiang, et al[38]	2014	"Ranibizumab 0 .3 or 0. 5 mg monthly treatment was more effective for neovascular AMD than non-anti-VEGF treatments but is no better than bevacizumab."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Schmucker, et al[43]	2011	"The bevacizumab studies show too many methodological limitations to rule out any major safety concerns. Higher evidence from ranibizumab trials suggests signals for an increased ocular and systemic vascular and haemorrhagic risk which warrants investigation."	Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.
Cheng, et al[34]	2012	"The strength evidence suggests that the intravitreal use of anti-VEGF antibodies is not associated with an increased risk of arterial thromboembolic events."	Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.
Schmucker, et al[41]	2012	"Evidence from head-to-head trials raises concern about an increased risk of ocular and multiple systemic AE with bevacizumab."	Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.

Vitamins and/or minerals (n = 7)			
Chong, et al[35]	2007	"There is insufficient evidence to support the role of dietary antioxidants, including the use of dietary antioxidant supplements, for the primary prevention of early AMD."	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). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Evans[36]	2008	"Current evidence does not support the use of antioxidant vitamin supplements to prevent AMD. People with AMD, or early signs of the disease, may experience some benefit from taking supplements as used in the AREDS trial. Potential harms of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (b-carotene), heart failure in people with vascular disease or diabetes (vitamin E) and hospitalisation for genitourinary conditions (zinc)."	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). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Evans, et al[21]	2012	"There is accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. There is no evidence with respect to other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations. Although generally regarded as safe, vitamin supplements may have harmful effects and clear evidence of benefit is needed before they can be recommended."	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). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Evans, et al[22]	2012	"People with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation."	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). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Hodge, et al[37]	2007	"Clinical research on this topic is scarce. Only two studies were eligible to be included in this review. Although one study result indicated efficacy of [omega-3 fatty acids] preventing AMD progression to its advanced form, this result needs to be duplicated and supported by future research."	The addition of omega-3 supplementation (DHA and EPA) had no further benefit.
Lawrenson, et al[27]	2012	"Until data from RCTs become available for analysis, there is currently no evidence to support increasing levels of omega 3 LCPUFA inthe diet for the explicit purpose of preventing or slowing the progression of AMD."	The addition of omega-3 supplementation (DHA and EPA) had no further benefit.
Evans[20]	2013	"The question as to whether people with AMD should take Ginkgo biloba extract to prevent progression of the disease has not been answered by research to date."	Not addressed in guideline
Photodynamic therapy (n = 5)			
Husereau, et al[63]	2002	"The evidence from three high-quality RCTs suggested that verteporfin PDT treatment for 2 years reduces the number of cases of central blindness, compared with placebo, by slowing disease progression. However, this treatment is not aimed at restoring vision and the majority of treated patients will continue to lose visual acuity. Verteporfin treatment did not increase serious adverse events compared with placebo (angiography and sham treatment), however, some adverse events occurred with greater frequency in individuals treated with verteporfin. The authors stated that these results relate to a study population with subfoveal neovascularisation from AMD, of which only a minority would be likely to qualify for treatment after diagnosis and angiographic assessment."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Oliva[65]	2002	"The scientific evidence suggests that PDT may be effective and safe for subfoveal CNV secondary to AMD."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Meads, et al[64]	2003	"There is a need to conduct a large, multicentre, publicly funded pragmatic double-blind RCT with parallel health economic evaluation to assess not just the impact of PDT on visual acuity and adverse events, but also directly measured global quality of life and survival. There is no indication of the relationship between benefits and costs where wet AMD affects the worse-seeing eye first. Treatment of wet AMD, with verteporfin, other types of PDT, and other new technologies is an area under very active investigation, so this technology should be kept under close review."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Meads, et al[40]	2004	"For several reasons it was considered that the most likely estimate of the predominantly classic subgroup effect size was the whole trial result. This has implications for the relationship between cost and benefit, the subject of intense debate. Results of the ongoing trials should help to clarify this subgroup effect size issue."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.

Wormald, et al[33]	2007	"Photodynamic therapy in people with choroidal neovascularisation due to AMD is effective in preventing clinically significant visual loss with a relative risk reduction of approximately 20%.Modified treatment regimens have not convincingly shown increased effectiveness. There was no evidence on quality of life and little on cost."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Laser photocoagulation (n = 2)			
Virgili, et al[31]	2007	"In the medium to long term laser photocoagulation of CNV slows the progression of visual loss in people with neovascular AMD. However, it is associated with an increased risk of visual loss immediately after treatment and this period may be longer in people with subfoveal AMD. With the advent of modern pharmacological therapies, and concern for the impact of iatrogenic scotoma in subfoveal CNV, laser photocoagulation of subfoveal CNV is not recommended. No studies have compared photocoagulation with modern pharmacological agents for AMD for non-subfoveal CNV."	Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment. Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy.
Parodi, et al[28]	2009	"The trials included in this review confirm the clinical observation that laser photocoagulation of drusen leads to their disappearance. However, there is no evidence that this subsequently results in a reduction in the risk of developing CNV, geographic atrophy or visual acuity loss."	Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment. Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy.
Submacular surgery (n = 2)			
Eandi, et al[19]	2008	"There is insufficient evidence from randomised controlled trials on the effectiveness of macular translocation, which is also not free of important risks. Furthermore, this technique is difficult to perform and a long surgical training is required. Future studies might include patients with small neovascular lesions that failed to respond to current pharmacological therapies and are willing to accept the risks associated with surgery to try to improve visual acuity."	Radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal steroids with verteporfin PDT are not recommended.
Giansanti, et al[26]	2009	"There is no benefit with submacular surgery in most people with subfoveal choroidal neovascularisation due to AMD in terms of prevention of visual loss. Furthermore, the risk of developing cataract and retinal detachment increases after surgery."	Radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal steroids with verteporfin PDT are not recommended.
Complement inhibitors (n = 1)			
Williams, et al[32]	2014	"There is insufficient information at present to generate evidence-based recommendations on the potential safety and efficacy of complement inhibitors for prevention or treatment of AMD. However we anticipate the results of ongoing trials."	Not addressed in guideline
Interferon alpha (n = 1)			
Reddy, et al[29]	2006	"At present there is not enough evidence to recommend the use of interferon alfa-2a for the treatment of age-related macular degeneration."	Not addressed in guideline
Radiotherapy (n = 1)			
Evans, et al[23]	2010	"This review currently does not provide convincing evidence that radiotherapy is an effective treatment for neovascular AMD. If further trials are to be considered to evaluate radiotherapy in AMD then adequate masking of the control group must be considered."	Radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal steroids with verteporfin PDT are not recommended.
Rheophoresis (n = 1)			
Wild, et al[46]	2009	"No evidence for the efficacy of rheophoresis in the treatment of patients with dry AMD."	Not addressed in guideline
Statins (n = 1)			
Gehlbach, et al[24]	2012	"Evidence from currently available RCTs was insufficient to conclude that statins have any role in preventing or delaying the onset or progression of AMD."	Not addressed in guideline
Steroids (n = 1)			
Geltzer, et al[25]	2013	"Based on the included trials, we found no evidence that antiangiogenic steroids prevent visual loss in patients with neovascular AMD."	Not addressed in guideline
Self-management programs (n = 1)			
Lee, et al[39]	2008	"Self-management programs appear effective for older adults with AMD. Small sample size, use of nontraditional statistics and methodological quality meant only a narrative analysis was possible. Future studies with more robust methodology including intent-to-treat analysis are still required."	Not addressed in guideline