The Royal College of Ophthalmologists

Age-Related Macular Degeneration:
Guidelines for Management

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[Click here to view the College Statement on choice of anti VEGF agents for wet AMD treatments *(February 2014)*]

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AMD Guidelines Group

Age-Related Macular Degeneration: Guidelines for the Management

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2. Rationale for the guidance

Age-related macular degeneration (AMD) is the commonest cause of severe visual impairment in older adults in the developed world. The two main late AMD phenotypes geographic atrophy and exudative AMD are responsible for two-thirds of registrations of visual impairment or blindness in the UK. It is estimated a quarter of a million older adults in the UK alone suffer from blindness due to this condition (1).

The past decade has witnessed an increase in therapeutic options with novel strategies to target neovascularisation without damaging the neural retina or other equally important tissues. The management of AMD continues to be a fast changing field. Since publication of the last guidelines, data have emerged which

have advanced our understanding of AMD and its management, and novel solutions have evolved to meet the ongoing challenge of AMD service demands. There are therefore compelling reasons to update the guidelines. Estimates from The Royal National Institute of the Blind and National Institute of Health and Clinical Excellence indicate there may be 26,000 people with exudative AMD now eligible for treatment in the UK each year- therefore given a total UK population of 60 million this would equate to 450 new cases per million per year

The guidelines are intended to set the standards for best practice in the NHS and in the private sector. They will be useful for education of ophthalmic trainees and those in other disciplines. The guidelines are also intended to give patients, carers and consumer organisations a resource with improved current information. The guidelines will act as a benchmark for service planning by providers, guide purchasers in the commissioning of services and set national standards for audit.

We have not rated the quality of evidence cited, but have described the study design in many cases.

3. Sources of information

Contributors identified relevant literature from a range of sources: Pubmed, the Cochrane Library, Current Contents and their own personal collections.

4. Epidemiology

4.1 Definitions

Age-related macular degeneration (AMD) is the term applied to ageing changes without any other obvious precipitating cause that occur in the central area of the retina (macula) in people aged 55 years and above (1) . In the early stages lipid

material accumulates as deposits beneath the retinal pigment epithelium (RPE) and within Bruch's membrane. When focal collections of lipid material are present these are referred to as drusen and can be seen as pale yellow deposits on a clinical examination of the retina. The retinal pigment epithelium also undergoes morphological alteration seen clinically as areas of hyperpigmentation and hypopigmentation. Generally drusen and RPE irregularities are not associated with disturbances of central visual function. A proportion of people (12.9 and 17.8% respectively) (2) with these early changes will progress to advanced AMD. When vision loss occurs it is usually due to the development of geographic atrophy and/or exudative disease.

Geographic atrophy (GA) is a sharply demarcated area of partial or complete depigmentation reflecting atrophy of the retinal pigment epithelium. The margins of the de-pigmented area are usually scalloped and the large choroidal vessels are visible through the atrophic RPE.

Exudative disease is also termed neovascular AMD. In the vast majority of eyes with neovascular disease, new blood vessels that have their origin from the choroid (choroidal neovascularisation (CNV)) are seen. CNV breaches the normal anatomical barrier of Bruch's membrane and invades the subpigment epithelial and or subretinal spaces. Neovascularisation can also arise de novo in the macular retina and is referred to as retinal angiomatous proliferation (RAP). RAP can establish contact with choroidal vessels to form chorioretinal anastomoses (CRA). Regardless of origin whether retinal or choroidal, the new vessels are unlike normal retinal vessels in that they are fenestrated and allow blood constituents to leak out. This egress of blood and serum causes the separation of Bruchs, RPE, and retina from each other and also results in the accumulation of intraretinal fluid the consequence of which is a generalised thickening of the retina or the formation of cystic spaces. These pathological manifestations cause the photoreceptors to become misaligned and eventually degenerative changes occur with cell loss and eventual fibrosis. The final result

is a scar often with a circular shape and hence the term disciform macular degeneration.

Idiopathic Polypoidal Choroidopathy (3, 4) is considered a variant of AMD. It consists of neovascularisation, primarily located within the choroid. It shares some features with AMD; for example it involves the macula, it is seen in the same age-group, it shares common non-genetic risk factors, such as smoking and hypertension and it shares common genetic risk factors such as CFH and ARMS2. However in contrast to AMD, polypoidal choroidopathy is seen in a younger age-group than AMD, it more often occurs in the nasal macula and the polypoidal neovascular complexes may leak and bleed but are less likely to invade the retina than CNV.

4.2 Classification

There are a number of classification schemes for AMD. The aim of these schemes is to provide a common nomenclature so that the prevalence of AMD and its development over time can be compared between different studies often undertaken in widely differing geographical locations. The main classification schemes share many similar features and are largely based on the Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS) (5). This grading system is based on the presence and severity of the characteristic features of AMD namely drusen, pigmentary irregularities, GA and neovascularisation. The WARMGS has been in use for over 2 decades and owing to its complexity and multiple scales attempts have been made to simplify it for use in both research and clinical situations. The first attempt to undertake this was in the mid-nineties when a consensus group met and developed the early age-related maculopathy (ARM) international classification system (6). This system attempted to distinguish the early features of macular ageing namely drusen and pigmentary irregularities from the late features of GA and CNV by using the term age-related maculopathy to signify only early disease. This has now come to be known as early age related macular degeneration.

1.1.1 Early Age Related Macular Degeneration

Features of early age related macular degeneration include:

- Soft drusen ≥ 63 μm (drusen are discrete lesions consisting of lipids and protein deposited under the retina (7))
- Areas of increased pigment or hyperpigmentation (in the outer retina or choroid) associated with drusen
- Areas of depigmentation or hypopigmentation of the retinal pigment epithelium (RPE)

4.2.2 Late Age Related Macular Degeneration: Geographic atrophy (GA) or Neovascular AMD, wet AMD, disciform AMD or exudative AMD)

Late age related macular degeneration is another term used for the late stages namely GA or neovascular AMD (nvAMD). A description of the clinical features of GA is given in section 4.1.1.

Clinical features that indicate the presence of nAMD include any or all of the following when these are seen within the macular area of the fundus. Intraretinal, subretinal or sub –RPE haemorrhages and/or fluid with or without peri retinal fibrosis in the absence of other retinal (vascular) disorders.

Both WARMGS and the ARM classification system give considerable details on size and surface features of drusen and the presence and absence of pigmentary irregularities. The longitudinal epidemiological studies which used these classification systems developed severity scales based on the multiple combinations of these features in order to predict progression to late AMD. Although the severity scales are moderately good at predicting the progression from early to late AMD, these groupings cannot be achieved without standardised systematic grading of stereoscopic fundus images, thus restricting their applicability in the clinical setting. The development initially of a 4 stage clinically achievable classification followed by the development of a simple risk prediction algorithm has been greeted with enthusiasm (8). The Age Related Eye

Disease Study (AREDS) is an ongoing randomised controlled clinical trial of dietary supplements in some 4000 participants ranging from persons with no evidence of early or late AMD in either eye to those with late AMD in one eye (9) (see also sections 6.1.4 and 6.2.3). Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.

The 4 stage classification of AMD from AREDS is shown below:

- No AMD (AREDS category 1) none or a few small drusen (<63 microns in diameter)

- Early AMD (AREDS category 2) any or all of the following: multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or RPE abnormalities.

- Intermediate AMD (AREDS category 3) any or all of he following: extensive intermediate drusen, and at least one large druse (≥ 125 microns in diameter), or geographic atrophy not involving the centre of the fovea.

- Advanced AMD (AREDS category 4); GA involving the fovea and/or or any of the features of neovascular AMD.

Prevalence

In a recent study using data from 31 population based studies from populations described as similar to the middle-aged and older populations of the UK, involving over 50 000 individuals in total, point estimates were made of the prevalence of late AMD. Using this methodology for the UK population resulted in an estimated prevalence of late AMD of 4.8% (95% CI 3.4% to 6.6%) of those over 65 years of age and 12.2% (95% CI 8.8% to 16.3%) of those aged 80 years or more in the UK (10). The same study predicted the prevalence of late AMD would increase by one third from 2010 to 2020. It is pertinent to note that the incidence of legal blindness attributed to AMD in Denmark has fallen by 50%

from 2000 to 2010, with most of the reduction occurring after the introduction of anti-VEGF agents for neovascular AMD (11).

Practical Points

The AREDS classification of macular degeneration into early, intermediate and advanced forms is of value when discussing vitamin supplementation.

AREDS revealed a beneficial effect of very high doses of antioxidants (daily dose vitamin C 500mg, vitamin 400 IU, Beta-carotene 15mg (25,000 IU)) and zinc 80mg (along with 2mg copper to prevent anaemia) in reducing patient's relative risk of progression to advanced AMD by 25%. These supplements may be indicated in patients with advanced AMD in the fellow eye (see also sections 6.14 and 6.2.3).

A history should always be taken to identify risk factors for advanced AMD, to aid in estimating prognosis and counselling.

5. Diagnosis

5.1 Clinical

Geographic atrophy. The presentation of GA is usually insidious and often detected during routine fundus examination. When GA is bilateral and involves the fovea of both eyes, patients may complain of deterioration of central vision. A common mode of presentation is difficulty with reading initially with the smallest sizes of print and then later with larger print and or words. The confirmation of the diagnosis of GA is by clinical examination using a high definition fundus lens for stereo biomicroscopy. This will reveal the characteristic area or areas of pallor with sharply defined and scalloped edges. When the area of GA is larger than 500 microns, large choroidal vessels are clearly visible within the area of pallor.

Usually areas of drusen and focal hyperpigmentation are visible in the retina adjacent to the patch of GA. Several imaging modalities may be useful, in particular fundus autofluorescence, in the evaluation of GA (12). Fundus autofluorescence along with spectral domain OCT has made it easier to diagnose GA, as these imaging modalities can reveal areas of GA that may not be clinically visible on biomicroscopy.

Exudative AMD. The commonest symptoms typical of onset of exudative AMD are central visual blurring and distortion. Most patients will complain that straight lines appear crooked or wavy. Sometimes patients do not notice visual symptoms when the first eye is affected. When exudative AMD occurs in the second eye, patients suddenly become unable to read, drive, and see fine detail such as facial expressions and features. This symptom described by many with AMD of a central dark patch in the visual field noticed at night, which clears within a few minutes as they adapt. Can also be present in patients with AMD who do not necessarily develop exudative AMD.

Examination of the macula usually reveals an exudative macular lesion along with other features of early AMD such as drusen and pigmentary irregularities. Sometimes these latter features are not visible once exudative AMD has supervened. However the fellow eye, if free of advanced disease, will often exhibit some or all of these early clinical signs and their presence is helpful in supporting the diagnosis that the neovascular lesion is due to AMD. Following slit lamp biomicroscopy the presence or absence of the following signs should be noted:

- Subretinal or sub-RPE neovascularisation which may be visible as grey green lesions. Occasionally the lesion will have a dark pigmented edge which is thought to be due to proliferation of the RPE at the edge of the membrane.
- Serous detachment of the neurosensory retina.
- RPE detachment.

- Haemorrhages- subretinal pigment epithelial, subretinal, intraretinal or pre-retinal. Breakthrough bleeding into the vitreous may also occur.
- Hard exudates (lipids) within the macular area related to any of the above, and not related to other retinal vascular disease.
- Epiretinal, intraretinal, subretinal or sub-pigment epithelial scar/glial tissue or fibrin-like deposits.
- Retinal angiomatous proliferations and retinochoroidal anatastamosis.

Idiopathic Polypoidal Choroidopathy (IPC) (see Section 4.1). This is an atypical form of neovascular AMD in which highly exudative lesions with steep walled haemorrhagic pigment epithelial detachments are seen most typically adjacent to the optic disc, but can occur anywhere within the macula and even outside the macula. High speed fluorescein or indocyanine green angiography typically reveals hyperfluorescent dilated complexes of choroidal vessels (branching vascular networks) that leak in the later phases of the angiograms. These dilated complexes look like polyps or grapes and hence the name. It was originally described in middle aged black populations and was more commonly seen in females. IPC is considered part of the spectrum of AMD and a strong association with hypertension and ischaemic heart disease has been described. The use of confocal high speed imaging devices allows IPC to be diagnosed more frequently and IPC accounts for more than a third of serosanguinous maculopathy in older adults in Asian populations and for 8-13% of that seen in Caucasians (3).

5.2 Conditions mimicking AMD

A number of disorders can result in macular lesions which have to be distinguished from AMD.

Exudative Macular lesions mimicking AMD.

- Diabetic maculopathy. This is the most common exudative central macular disorder in older adults. Patients with diabetes frequently exhibit retinal microaneurysms, haemorrhages and exudates often in the context of macular oedema. The presence of more extensive vascular signs outside the macular arcade along with venous engorgement or beading should alert the clinician to a diagnosis of diabetic maculopathy. The visual function is less markedly reduced in eyes with diabetic maculopathy when compared to eyes with CNV involving the fovea. Fluorescein angiography is needed to confirm the absence of choroidal neovascularisation and sub RPE pathology. Sometimes exudative AMD and diabetic maculopathy can coexist as both are common conditions.
- High myopia can be associated with choroidal neovascularisation. These neovascular complexes are believed to occur as a consequence of the development of minute cracks in thinned Bruchs membrane allowing choroidal vessels to access the subretinal space.
- Inflammatory CNV. A number of the choroidal inflammatory white dot syndromes (eg. Presumed ocular histoplasmosis, punctate inner choroidopathy, multifocal inner choroidopathy) can be associated with inflammatory choroidal neovascularisation.
- Central Serous Chorioretinopathy (CSR) This is characterised by a collection of serous fluid in the sub-neurosensory retina without any evidence of neovascularisation. Chronic CSR can sometimes be confused with AMD, again the history, symptoms and a combination of retinal imaging usually helps distinguish between the two. CNV and IPCV can occur as a complication of chronic CSR.
- Macular telangiectasia. Idiopathic macular telangiectasia (13) (MACTEL) also sometimes termed perifoveal or juxtafoveal telangiectasia may be difficult to distinguish from nAMD, particularly with the RAP form of n AMD. In Two types of telangiecgtasia have been described in the MACTELstudy Type 1 MACTEL occurs in middle age persons; the condition is usually unilateral and exhibits exudative features as the vessels are leaky and intraretinal fluid accumulation occurs with a cystic maculopathy and surrounding exudates. Type 2 MACTEL

occurs in older people and is usually bilateral with evidence of crystalline deposits, pigmentary charges, and right angled venules evident temporal to the fovea and extending to the entire perifoveal region. While leakage is detectable on fluorescein angiography, there is no evidence of increased retinal thickening. Cystic spaces are evident within the retina using OCT and these spaces are thought to reflect the loss of retinal tissue. Occasionally, sub-retinal neovascularization develops and arises from the retinal circulation (14).

Non exudative macular lesions mimicking AMD

- Pattern dystrophy (PD) affects the macula and can be mistaken for nonexudative AMD. The most common types of PD seen are adult vitelliform macular dystrophy (AVMD) and less commonly butterfly shaped pattern dystrophy. PD is a condition which has a genetic basis; although a family history is often not present. PD is usually associated with a better visual outcome than AMD, unless complicated by choroidal neovascularisation or atrophic changes. Differentiating AVMD in particular from AMD can be difficult. Symptoms may be similar particularly if CNV or atrophy complicates PD, but often AVMD is identified in an asymptomatic individual at a routine fundoscopic review. Fundus autofluorecence imaging especially when combined with optical coherence tomography is helpful in distinguishing PD from AMD. Fluorescein angiography can show a typical ‘corona sign’ in AVMD, and the branching lines seen in butterfly shaped PD are associated with a hyperfluorescence distributed in the area of the deposits, which does not show leakage throughout the phases of the angiogram. Occasionally, fluorescein angiographic staining of the vitelliform lesion can be mistaken for active leakage from CNV.

5.3 Retinal imaging

Retinal imaging is an integral part of patient management and is required for diagnosis and monitoring response to therapy. Commonly used retinal imaging techniques are colour fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT),

and fundus autofluorescence (FAF). Previously fundus photography and FA were undertaken using traditional fundus cameras and the images were captured on 35 mm film. However there has been almost complete transition to digital acquisition systems since the advent of high resolution digital cameras, marked improvements in electronic capture and storage systems with corresponding advances in image capture software and increased capacity for storage. in. Important advantages of digital angiography are the ability to instantaneously display captured images for review prior to saving them, use of standardized software to measure areas of interest, easy archiving, storage and retrieval of the images.

5.3.1 Fundus photography

Colour fundus photography provides a record of the appearance of the macular retina. Stereoscopic images of the macula viewed appropriately can help localise pathology to the different tissue layers. For the purposes of recording macular pathology stereoscopic pairs of images taken at 35 degrees centered on the macula are recommended.

5.3.2 Fundus Fluorescein angiography (FFA)

FFA is currently the gold standard for diagnosing CNV in AMD. An FFA is a sequence of images captured of the fundus over a 10 minute period after injection of the non-toxic dye fluorescein isothiocyanate into a suitable peripheral vein.

In the 1980's fluorescein angiography (FA) was typically undertaken using analogue capture on 35 mm film. FFA on film produces a negative picture with the hyperfluorescence visualised as black areas. The film can be printed to give a positive image in which hyperfluorescence is visualised as a bright area but with a loss of image quality. Digital images are now the most commonly used, and are 'positive' therefore hyperfluorescence is seen as a bright area.
Colour photographs must accompany the FFA as they yield important additional information on the composition of the macular lesion allowing interpretation of the

FFA. Haemorrhage, pigment and exudate are easily distinguished from each other on colour images all but are seen as dark areas on FA . Early phases of the angiogram must be captured as they are important for the visualization of the choroidal phase and the early arterial phases when pathology is better seen before obscuration of details by leakage and pooling of fluorescein dye.
Late images (10 minutes) are also important for distinguishing late leakage from drusen (which can take up fluorescein but which fade towards the end of the fluorescein run) and RPE window defects, and inactive scars. This is necessary to distinguish active from inactive pathology, which may be important for initiating or continuing treatment.

Stereo images are necessary to identify the tissue compartment in which pathological features are seen e.g. RPE elevation, and/or elevation of the neurosensory retina.

Preparation for FFA: It is important to document a patients' medical history and obtain consent. The history should elicit any fluorescein allergy noted at a previous exposure. If indocynanine green angiogram is also requested, any allergy to iodine or shellfish must be checked. A record of the patient's current medications should be made and blood pressure recorded. While existing cardiovascular or renal disease (or liver disease in ICG use) are not reasons for withholding angiography, this information may prove useful in terms of subsequent patient management particularly in the event of an allergic reaction. If a patient is known to have a mild history of allergy from a previous FA, one may still be performed after taking appropriate precautions such as administration of an appropriate drug e.g. an antihistamine such as chlorpheniramine (Piriton). Serious adverse reactions are extremely rare (15). Yannuzzi et al estimated the risk of death following FA to be 1: 222 000 (16). It is essential therefore that the facilities for resuscitation with a standard protocol should be available. If a patient has a minor allergic reaction observation for at least 30 minutes is recommended before they leave the unit, as more severe life

threatening reactions may take time to develop. While units perform FFA differently the following is a typical protocol that can be used;

- Obtain consent.
- Fill out patient proforma.
- Dilate both pupils for photography.
- A cannula should be sited in a suitable peripheral vein and its location checked to ensure that there is no danger of extravasation.
- The photographer should take the colour stereo pairs of the macular retina and red free images as required and prepare the camera for fluorescein capture by introducing the appropriate filter and barrier lenses.
- A nurse or other qualified personnel should check the patency of the venflon and then inject 2.5 or 5 mls of 10% or 20% Sodium fluorescein through the venflon. Injecting fluorescein quickly facilitates interpretation of the resulting images.
- The photographer starts the timer and captures images as stereo pairs of the macula of the eye in question with a sideways movement of the joystick between pairs (no rotation, change in focus or swivelling of the camera is allowed between capture of the members of one pair). If one eye only is the focus of interest then images are captured of this eye until 60 seconds have elapsed. Rarely the clinician may wish early pairs of both eyes and in this event the photographer may be instructed to obtain stereo pairs of the fellow eye around 25 to 30 seconds after the run has commenced. Usually stereo pairs are obtained of each macula at 1 min, 2 mins, 5 mins and 10 mins.
- The photographer reviews the run, deletes unwanted or poorly focused images and saves the rest for archiving.

5.3.3 Angiographic features of neovascular AMD

Neovascular lesions are classified by their location with reference to the foveal avascular zone – extra-foveal, juxtafoveal or subfoveal. Lesions lying more than

200µm from fixation are defined as extrafoveal, while those immediately adjacent to or involving the geometric centre of the fovea are juxtafoveal or subfoveal respectively. Neovascular lesions located away from the macula are termed peripheral or juxtapapillary depending on their location. This classification system had more relevance before the advent of anti-vascular endothelial growth factor agents (antiVEGFs) as the location of the neovascular lesion has no bearing on whether anti-VEGF treatments are given or not.

A more detailed classification of the neovascular lesion includes a description of the composition of the exudative lesion after stereoscopic review of the entire sequence of the angiogram. The exudative lesion is defined as the area occupied by the neovascular complex, any associated blood, thick exudate and pigment epithelial detachments that are contiguous to the vessels and obscure its margins. It is now appreciated that the neovascular complex can consist of retinal angiomatous proliferation (RAP), choroidal neovascularisation (CNV) or idiopathic polypoidal choroidal vasculopathy (IPC) The initial classification of nAMD lesions was derived by the macular photocoagulation study (MPS) group prior to the recognition of RAP and IPC as AMD entities. The MPS classification remains helpful and allows CNV to be classified based on the temporal and spatial features of the patterns of fluorescence as observed on the FA (17). A description of these features is given below.

Classic CNV is said to be present when an area of well-delineated hyperfluorescence appears in the early phases of the FA usually before 30 seconds have elapsed following injection of the fluorescent dye into a peripheral vein. Classic CNV represents new vessels that have breached the RPE and lie in the subretinal space. Sometimes a typical lacy pattern of hyperfluorescence is observed in the very early phase of the angiogram which corresponds to the vascular profiles before the fluorescein has leaked out of these vessels and obscured the margins. Classic CNV also leak aggressively and hence there is considerable pooling of fluorescein dye in the sub retinal space.

Occult CNV as its name suggests is the presence of leakage without clear evidence of neovascular profiles in the early angiographic images. Two types of occult leakage are recognised. The first is a characteristic stippled hyperfluorescence which occurs early and is located at the level of the RPE. The RPE layer is elevated and in the later phases of the angiogram there is increasing hyperfluorescence and pooling of dye in the subretinal pigment epithelial space. The pattern of leakage suggests new vessels between Bruch's membrane and the RPE and it is therefore considered to be a fibrovascular pigment epithelial detachment (FPED). The second pattern of occult leakage is a more diffuse hyperfluorescence with poorly demarcated boundaries which occurs late in the angiographic phase generally after 2 minutes have elapsed since injection of dye. There is no corresponding hyperfluorescence in the early frames and there is shallow elevation of the RPE. This type of leakage is referred to as late leakage of indeterminate origin (LLIO).

Many lesions are mixed showing combinations of classic and occult features.

It is now common practice to classify lesions by presence or absence of classic and or occult CNV. In the absence of any occult CNV, lesions are termed classic with no occult (100% classic) and conversely occult with no classic (0% classic). When CNV are mixed the lesion is classified by the proportion of classic. When the lesion is composed primarily of classic CNV (i.e. classic greater than 50%) it is termed predominantly classic. When there is 1 to 49% classic the lesions are termed minimally classic.

Prior to the advent of OCT Gass also classified choroidal neovascular membranes into two types according to their anatomical site (18). Type 1 membranes are present in the subretinal pigment epithelial space and their excision results in a large retinal pigment epithelial defect. Type 2 membranes are present in front of the retinal pigment epithelium and may be excised without significant damage to the retinal pigment epithelium. Type 2 choroidal neovascular membranes are typically found in children and young adults and therefore associated with conditions such as presumed ocular histoplasmosis,

punctate inner choroidopathy, multifocal choroiditis, high myopia, angioid streaks and choroidal rupture.

One type of neovascularisation that has been recognised by the use of high speed video angiography using the scanning laser ophthalmoscope is the RAP lesion. RAP's are seen as intraretinal telangiectatic and tortuous blood vessels within the macula. On viewing stereo pairs of images, the vessels are seen to turn sharply from the inner retina towards the choroidal interface. RAP's are commonly associated with large serous PEDs and extensive areas of small drusen. They leak aggressively and hence the adjacent retina is usually disrupted with cystoid spaces.

Serous PEDS can also arise in the absence of vascularisation and ICG angiography is a useful tool for distinguishing vascularised from non-vascularised PEDs. Non-vascularised PEDs are thought to arise because Bruch's membrane is altered by changes such as free radial or oxidative damage and degeneration of collagen and elastin, resulting in separation of the RPE from Bruchs.

Idiopathic polypoidal choroidopathy (3, 4) (IPC) (see Section 4.1) is another component of the spectrum of exudative AMD. IPC are seen as focal areas of abnormal dilated choroidal vessels and result in a highly exudative picture with considerable accumulation of lipid and or haemorrhage in the subretinal space. These are best visualised by ICG angiography.

5.3.4 ICG angiography

Indocyanine green (ICG) is an alternative dye to fluorescein which is used to visualize the choroidal circulation. This dye binds to plasma protein and hence does not egress through the fenestrae of the choroidal vessels, instead remaining within the vascular compartment. Choroidal vessel morphology is therefore better delineated. ICG is imaged using infra red wavelengths which can pass through the RPE and blood therefore permitting visualization of pathology which can block the transmission of wavelengths that excite fluorescein. The usefulness of ICG is limited if there is very thick blood or pigment as this can

reduce or block transmission of the infrared wavelengths; the emitted light is of lower intensity compared with fluorescein. The use of the scanning laser ophthalmoscope (SLO) with video capture can however yield images of high resolution. Video ICG also allows better imaging of RAP. As ICG dye does not leak into the subretinal and subpigment epithelial spaces to the same extent as fluorescein the enhanced definition of the vascularised tissue as a hotspot is possible and a combination of FFA and ICG can produce complementary information. A dose of 25mg of ICG in aqueous solution is usually injected intravenously and images acquired for up to 30 minutes.

5.3.5 Ocular coherence tomography (OCT)

Optical coherence tomography (OCT) relies on the analysis of wave patterns of reflected laser light to produce an image. A reflectivity profile called an A scan is generated. Early commercial OCT's (time domain OCTs) captured around 100 A scans a minute and had a resolution approaching 30μm. The new Fourier Domain (FD) OCT's which capture around 20,000 A scans a minute have higher resolution permitting the visualization of retinal layers. Nonetheless the FD OCT can achieve a resolution of between 5 and 10 μm allowing more detail than ever before to be visualised. The multilayered structure of the retina is clearly visible and the RPE and Bruch's membrane are also partially delineated. Most incident light from the OCT is reflected before it reaches the RPE. While variations in RPE pigmentation may allow some light to reach the choroid this is insufficient to resolve choroidal structure in detail, although functions such as 'Enhanced Depth Imaging' facilitate assessment of choroidal features such as choroidal thickness. OCT is excellent at detecting separation of retina from the RPE and the RPE from its basement membrane and identifying interruptions in the RPE layer including a tear. Thickening of the retina and the presence of intra-retinal fluid are also easily detected. CNV are also easily visualized as these are seen as areas of high reflectivity and their relation to the tissue compartments, i.e. below the RPE, above the RPE or involving the neuroretina, can be judged. The composition of the tissue i.e. RPE proliferation, endothelial tubes (perfusing

CNV), fibrosis or organized haemorrhage cannot be ascertained as all of these tissue components appear to have similar reflectivity characteristics. The OCT poorly delineates the choroidal-RPE interface owing to poor penetration of light to that level.

In some OCT machines the registration of the image is dependant on a black and white fundus photograph taken at the same time, with others a SLO image is obtained with exact correlation with the OCT images and with other machines a pseudo- fundus image is obtained by re-constructing the OCT slices.

Some OCT imaging systems are combined with FFA and or ICG capabilities, which will improve correlation of the different information.

OCT may be used for screening the macula prior to performing more invasive imaging such as FFA. In certain cases OCT alone provides sufficient information to permit decisions on clinical management and follow up, for example an OCT may confirm a clinical impression of an adult vitelliform lesion by showing lack of leakage.

To obtain relevant information appropriate high quality scans with the more recent generation of OCT's are required, i.e. fourier domain. Appropriate protocols should be used and technicians should be trained in the acquisition of images. As such high speed spectral domain OCT machines perform many thousands of scans across the macula, being less vulnerable to movement artifact and blinking, pathology is less likely to be missed and the technology will contribute in distinguishing different diagnoses.

Emerging developments in OCT imaging technology, such as swept source OCT and adaptive optics, may promise even better images with resolution potentially down to the individual photoreceptor,but their place in clinical practice is yet to be determined.

5.3.6 Fundus Autofluorescence Imaging

This can give an indication of the health of the RPE. Autofluorescence is detected by confocal scanning laser ophthalmoscopy. Signals generated by excitation at short wavelengths originate mainly from lipofuscin, a collection of

by-products of the visual cycle found in RPE cells following RPE phagocystosis of outer segments. Increased autofluorescence represents accumulation of lipofuscin and suggests that the RPE cells are beginning to fail. Absence of autofluorescence results in a black image and is due to loss of RPE cells. While different patterns have been described in early and late AMD the exact utility of autofluorescence is under ongoing investigation. For example the finding of patches of absent autofluorescence may explain central scotoma patterns. Fundus autofluorescence imaging can be used for the evaluation of GA progression (19). In contrast patterns seen with near infrared fundus autofluorescence are begining to be recognised (20). It uses a higher excitation wavelength, such as that normally used during ICG angiography, and its signal is thought to originate from melanin in the RPE and choroid (21).

5.3.7 Structure function relationships

Increasingly imaging devices are being combined to allow better correlation of structure and function. Systems that perform a simultaneous acquisition of FFA and ICG on the SLO combined with OCT are now available commercially. Others have combined macular perimetry with colour imaging and/or OCT and ICG. Multifocal ERG is also possible (22). Spectral imaging indicating oxygen saturation in the retina and its vasculature is under investigation and adaptive optics is an exciting new development, which allows in vivo imaging of individual photoreceptors.

Practical Points

Stereoscopic fluorescein angiography is indicated to determine the extent, type, size and location of CNV.

ICG is useful when assessing patients with macular haemorrhage or suspected of having retinal angiomatous proliferative lesions, idiopathic polypoidal choroidopathy, or non-vascularised vs. vascularised PEDs.

High resolution OCT, such as spectral domain OCT, is mandatory for diagnosis and monitoring response to therapy.

6. Risk factors

Many risk factors have been identified for AMD (23), but published evidence for some is weak or inconsistent. Furthermore it is not practical to measure some factors, such as genetic or nutritional factors, in a clinical setting. Increasing age, current smoking, family history and cataract surgery are considered risk factors for advanced AMD though the effect of cataract surgery may at least partly be due to shared risk factors, such as age. Other factors moderately associated with AMD include cardiovascular disease, hypertension and higher plasma fibrinogen.

6.1 Ocular

6.1.1 Precursor lesions (also see section 4.1.1 and 4.1.2)

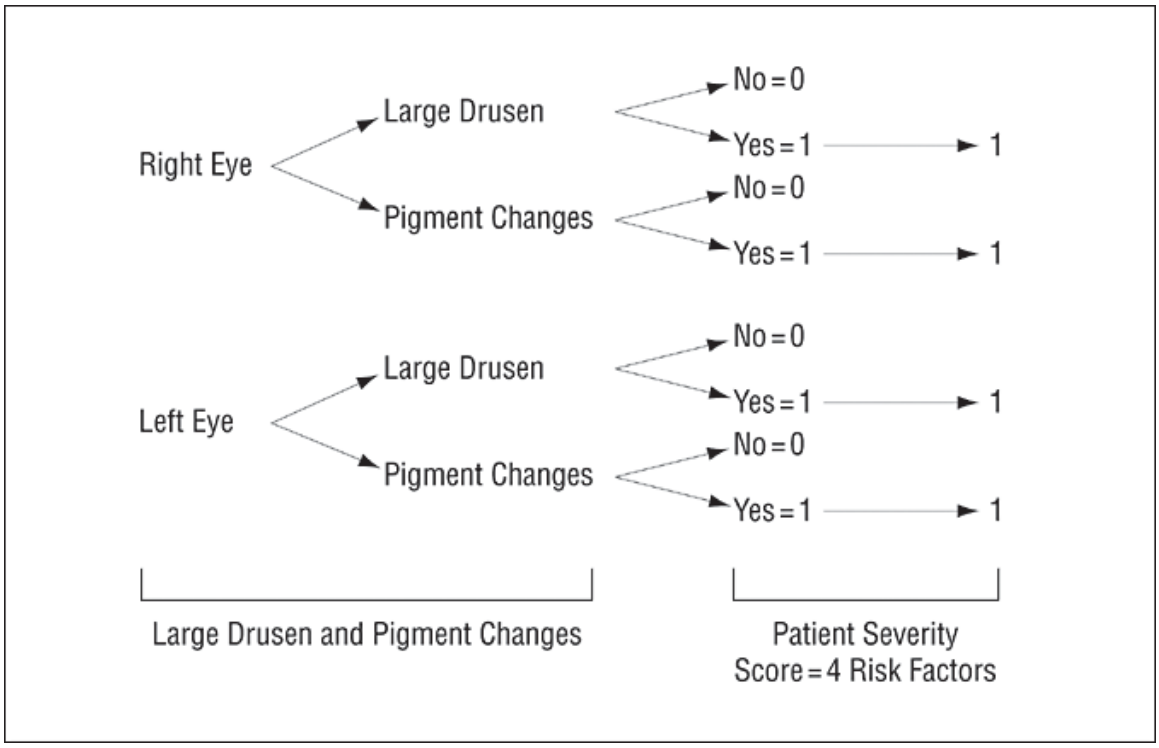
Drusen are commonly found in older people and are not always associated with progression to late AMD and visual loss. As mentioned previously the risk of progression from early AMD to late AMD has been analysed in participants of the AREDS study (see section 4.2.2) and a predictive algorithm suitable for clinical use has been developed (figure 1) (24). Three ocular factors predicted the progression of AMD: presence of large drusen (>125 microns which approximates the size of a normal retinal vein at the disc margin), retinal pigment epithelial abnormalities and the presence of late AMD in one eye. A five step score (0 to 4) was proposed which can be used to identify the approximate 5-year risk of developing advanced AMD based on these factors:

Score	Risk
0	0.5%
1	3%
2	12%
3	25%

4 50%

For people who have features of early AMD in one or both eyes namely large drusen or pigment abnormalities a score of 1 is assigned per feature per eye. In those people with advanced AMD in one eye, the 5-year risk for the development of advanced AMD in the fellow eye is estimated by assigning a score of 2 for existing GA or CNV in the first eye and to this is added to the scores for large drusen or pigment abnormalities in the second eye. Figure 1 shows how the overall score is computed.

Figure 1



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The following precursor lesions (sometimes referred to as early ARM) are risk factors for progression to advanced AMD (both nAMD disease and GA) (2, 25-27):

- large drusen
- soft indistinct drusen

- extensive drusen area
- hyperpigmentation.

A detailed description of the relationships between the above features and development of AMD is given in section 4.2. Until lately the presence of small hard drusen was not considered a risk factor for progression. However one recent study suggests that people with larger numbers of small hard drusen are at increased risk of developing soft indistinct drusen and pigmentary abnormalities (2). This suggests that there is a continuum from small hard drusen to advanced AMD.

6.1.2 Refractive status

A number of studies have reported an increased risk of AMD associated with hyperopia (28-32) but other studies have not (33-36). One prospective study has found a modest increase risk of AMD in people with hyperopia (32).

However the observed association between hyperopia and AMD may well be due to differential misclassification, for example, people with high myopia may be less likely to be classified as having AMD, or the classification of drusen may be different in people with hyperopia (37).

6.1.3 Iris colour

There is inconsistent evidence for an association between iris colour and development of AMD. Some studies have suggested that there is an association (28, 38-41). However others have not found such an association (33, 34, 42-45). The Beaver Dam Eye Study found an inconsistent relationship between iris colour and 10 year incidence of drusen and pigmentary abnormalities (46).

The systematic review and meta-analysis mentioned above showed no significant protective effect of any iris colour when three prospective studies were pooled, and also for the pooled results of two cross-sectional studies (23).

6.1.4 Macular pigment

Macular pigment is composed of two carotenoids, lutein and zeaxanthin, which are solely of dietary origin and which are found in a wide variety of green leafy plants such as spinach and kale and in some animal products such as egg yolks (47) It is thought that they protect the retina from the harmful effects of free radicals released by visible light (48, 49), though their monitoring in clinical practice may not be sensitive enough to be useful (50, 51).

Decreased serum, dietary and retinal levels of these carotenoids have been associated with an increased risk of AMD in some (30, 52-57) but not all observational studies (58-64). For example in AREDS, a higher dietary intake of lutein and zeaxanthin, measured using a self-administered food frequency questionnaire and divided into quintiles, was associated with a statistically lower risk of developing advanced AMD compared to having a lower intake (65). A trial on ninety subjects with atrophy AMD showed some functional benefit to supplementation with lutein in people with AMD (66). While lutein supplementation and increased macular pigment optical density have been associated (67) the relevance of this to AMD is not fully established.
While there is insufficient evidence to recommend lutein and zeaxanthin supplements, eating a diet rich in leafy green vegetables and fresh fruit is likely to improve concentrations of macular pigment in the fundus and is unlikely to do any harm. The Age-Related Eye Disease Study 2 (AREDS 2) was a multi-centre randomized trial of lutein, zeaxanthin and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) in preventing progression to advanced AMD in those at moderate to high risk of progression after five years of follow-up. No extra reduction in risk of progression to advanced AMD was evident in AREDS 2 by the addition of lutein and zeaxanthin, or DHA and EPA, or all of these to the AREDS formulation (68) (see also section 6.2.3).

6.2 Lifestyle

6.2.1 Tobacco smoking

Cigarette smoking is a well-established risk factor for the development of AMD (69-74). Current smokers have a two to three-fold increased risk of developing AMD and there is a dose-response relationship with pack-years of smoking (75-77). Those with a genetic susceptibility are also more likely to develop AMD if they smoke (see under 6.4.2). Tobacco smoking is the main modifiable risk for AMD. Public health interventions to help people stop smoking will play an important role in preventing the development of AMD (78). The meta-analysis mentioned above (23) found when the results of six prospective cohort studies were pooled, the relative risk of AMD for smokers was 1.86 (95% CI 1.27 - 2.73).

6.2.2 Alcohol intake

Alcohol consumption is a plausible risk factor for AMD because it is known to cause oxidative stress and damage to many organs in the body. However findings are inconsistent with some studies indicating increased risk while others indicated reduced risk (79-85). A systematic review and meta-analysis showed that heavy alcohol consumption was associated with an increased risk of early AMD whereas the association between heavy alcohol consumption and risk of late AMD was inconclusive (86). It is unlikely that alcohol consumption is an important risk factor for AMD.

6.2.3 Diet and nutrition

Antioxidant nutrients

The “free-radical” theory of ageing proposes that oxygen radicals damage cells over time (87). It is thought that the retina may be particularly vulnerable to oxidative stress because of a combination of exposure to visible light and high oxygen concentrations (49). Considerable interest has focused on whether foods high in antioxidant micronutrients may be protective for the development of AMD.

Carotenoids (in particular beta-carotene, lutein and zeaxanthin), vitamin C, vitamin E and zinc are all common in the diet and have antioxidant properties.

A number of studies have investigated the relationship between dietary intake (30, 54, 57, 59, 60, 62-64, 88-93) or serum levels (94-99) of antioxidant nutrients and risk of AMD with inconsistent results. Difficulties with interpreting these studies include the fact that people with diets rich in antioxidants may have different lifestyles from people with diets that are low in antioxidants.

A Cochrane review (100) on the effect on AMD progression of antioxidant vitamin and mineral supplements meta-analysed thirteen eligible studies, though most participants came from the Age-Related Eye Disease Study (AREDS) (9). AREDS was a randomised placebo controlled study on the effect of anti-oxidant supplements (500 milligrams of vitamin C; 400 IU of vitamin E; 15 milligrams of beta-carotene; 80 milligrams of zinc as zinc oxide; and two milligrams of copper to prevent copper deficiency which can result from high dose zinc supplementation) (see also section 6.1.4). AREDS found a reduced risk (adjusted odds ratio 0.68; 99% confidence intervals 0.53 to 0.87) of progression to advanced AMD in those with AMD who took antioxidant supplements for a mean of 6.3 years. A note of caution is necessary as the generalisability of results from AREDS from the relatively well nourished American population sampled to other populations is not clear, and while such dietary supplements are generally safe, harmful effects are possible.

Results of studies on the prevention of AMD using dietary means have been less encouraging. A systematic review of prospective studies of dietary intake found no evidence that diets high in antioxidant vitamins protect against AMD (100, 101). The Womans' Health Study investigated over 39000 subjects and found alternate day supplementation with 600IU of vitamin E did not significantly reduce the incidence of 'visually significant' or advanced AMD compared to placebo, after a mean of ten years follow-up (102). This study was included in a recently published Cochrane systematic review on the prevention of AMD in which four large high quality randomised trials cumulatively including 62520 participants were meta-analysed (100). The review provided evidence that taking vitamin E

and beta-carotene does not delay or prevent the onset of AMD, while stating that there is no evidence that anti-oxidant supplements prevent or delay the onset of AMD and cautioning that vitamin supplements may have harmful effects. Two large trials have shown that smokers who take beta-carotene may be at increased risk of lung cancer (103, 104). The Heart Outcomes Prevention Evaluation (HOPE) Study found that vitamin E supplementation was associated with an increased risk of heart failure in people with diabetes or vascular disease (105).

Polyunsaturated fatty acids

There are two groups of polyunsaturated fatty acids: omega-3 fatty acids and omega-6 fatty acids. The retina contains high levels of the omega-3 fatty acid docosahexaenoic acid (DHA), particularly in the disc membranes of the photoreceptors. The omega-3 fatty acid eicosapentaenoic acid (EPA) has beneficial effects on inflammation which is also implicated in the pathogenesis of AMD. A recent systematic review identified nine relevant studies of dietary intake of omega-3 fatty acids and AMD (106). A high dietary intake of omega-3 fatty acids was associated with a 38% reduction in the risk of late AMD (pooled odds ratio [OR], 0.62; 95% CI 0.48 to 0.82). Fish intake at least twice a week was associated with a reduced risk of both early AMD (pooled OR, 0.76; 95% CI, 0.64 to 0.90) and late AMD (pooled OR, 0.67; 95% CI, 0.53 to 0.85). The AREDS 2 trial (see also section 6.1.4) investigated supplementation with omega-3 long-chain polyunsaturated fatty acids (DHA and EPA) (68). No extra reduction in risk of progression to advanced AMD was evident in AREDS 2 by the addition of lutein and zeaxanthin, or DHA and EPA, or all of these to the AREDS formulation. Including oily fish in the diet is currently advised for other health reasons and may reduce the risk of developing AMD.

6.2.4 Obesity

Measures of obesity such as body mass index (BMI), waist circumference and waist-hip ratio have been measured in a number of studies. In general, reported findings suggest an increased risk of AMD with increasing BMI and abdominal obesity (107-109). In the AREDS study high BMI was associated with neovascular disease at baseline (110) but this association was not seen with follow up except with GA (111). Two studies have found evidence of a J-shaped curve and suggested that people with low BMI are also at risk (112, 113). Inconsistencies in relationships have been found and in one study BMI and waist-hip ratio were associated with AMD in women but not men (114) and in another study high BMI was associated with AMD in men and not women (36).

Although a review concluded that current research has not identified a consistent association between obesity and risk of age-related maculopathy (115) a more recent meta-analysis of seven prospective cohort studies and six cross-sectional studies found that increasing BMI was a risk factor for AMD (23). However the authors of the meta-analysis pointed out that the associations could have been due to shared risk factors (such as hypertension) or unmeasured confounders (such as nutritional status).

6.3 Medical risk factors

6.3.1 Hypertension

Hypertension plausibly increases the risk of AMD due to its effects on the choroidal circulation (116). It is noteworthy that reduced choroidal thickness is associated with both hypertension and AMD, though understanding of clinical factors affecting choroidal thickness is at an early stage. Raised blood pressure has been associated with AMD in some (110, 117-121) but not all (122-124) studies. A meta-analysis (23) found inconsistent odds ratios in studies testing association of hypertension and AMD, but a statistically significant odds ratio when studies were pooled (OR 1.48, 95% CI 1.22 - 1.78). There is no evidence that antihypertensive medication or treatments to lower blood pressure can prevent the development or progression of the disease.

6.3.2 Coronary and vascular disease

People with AMD may be at increased risk of coronary heart disease (120, 125), stroke (126) and cardiovascular mortality (127, 128). However, findings have been inconsistent: and some studies have found no association between history of cardiovascular disease and AMD (118, 129). A systematic review (23) found a significant association when studies were pooled (OR 2.20; 95% CI 1.49 - 3.26), although what constituted cardiovascular disease may varied across studies.

HMG CoA Reductase Inhibitors (statins) protect against cardiovascular disease by reducing dyslipidaemia (130). Some studies have suggested that people taking statins are at reduced risk of AMD (131-134) while others have not (135-137). A Cochrane review found insufficient evidence to make a judgement (138) on the efficacy of statins in preventing or delaying AMD onset or progression. A recent meta-analysis of observational studies concluded that lipid-lowering agents, including statins, do not appear to lower the risk of developing AMD (139).

6.3.3 Diabetes

Diabetes and AMD appear to be unrelated. Many studies have investigated this relationship but few studies have found any link (140). In the EUREYE study, participants with neovascular AMD were significantly more likely to have diabetes (odds ratio 1.81; 95% confidence interval, 1.10 to 2.98), though there was no association between early AMD and diabetes (141). The meta-analysis by Chakravarthy et al (23) showed an association of diabetes with late AMD when four prospective cohort studies were included, but mixed results were evident for case-control association studies.

6.4 Genetic risk factors for AMD

It is known that a family history of AMD is a risk factor for AMD (23). Multiple genetic variants have been reported to influence the risk of developing AMD, reviewed by Lotery et al (142). Some of these are relatively rare, contributing

genetic risk of small effect to a low number of patients. However, unlike other common diseases, AMD is relatively unusual in that several genes of large effect have been reported to affect a large fraction of patients. This is encouraging as it suggests that in the future, screening programs or gene-dependent treatments will be feasible as only a small number of genetic polymorphisms need to be assessed to identify genetic risk in a large number of patients.

6.4.1 Major genetic risk factors

The complement system is a powerful component of innate immunity which recognizes and facilitates the elimination of pathogens and unwanted host material. Since complement activity can also lead to host tissue injury and inflammation, strict regulation of the complement cascade is important.

In 2005 it was established that a mutation in a key regulator of the complement pathway: complement factor H (CFH) is strongly associated with risk of AMD (143-146). Carriage of the Y402H polymorphism in this gene increases the risk of developing AMD between 2 and 7 fold and accounts for up to 50 % of the population attributable risk of AMD. Identification of this association with AMD has re-defined AMD as a disease of complement dysregulation in roughly 50 % of patients. It is now recognised that variation in several genes which code for proteins involved in the complement cascade either significantly increases the risk of AMD (complement factor H (CFH) but also complement component 3 (C3) (147)) or can decrease the risk of AMD (complement component 2 (C2) and factor B (BF) and deletion of CFH-related genes CFHR1 and CFHR3). Collectively these genetic associations appear to implicate dysregulation of the alternative complement pathway in causing AMD. This insight is likely to lead to the development of novel therapies. In addition a link between the CFH Y402H mutation and oxidative stress has recently been discovered (148).
Single nucleotide polymorphisms (SNPs) in chromosome 10q26 are associated with an increased risk for AMD. However it is currently unresolved whether SNPs identified in the coding region of the LOC387715/ARMS2 (age-related

maculopathy susceptibility 2) gene (149), or located in the promoter region of HTRA1 (high temperature requirement factor A1) (150, 151) represent the true genetic risk variant at this locus. The function of the ARMS2 gene product is not known, while mapping evidence implicating HTRA1 is compelling because the gene codes for a serine proteinase. It is conceivable that excess degradation of extracellular matrix in the retina could facilitate the invasion by choroidal neovascularisation. However as these SNPS exist in strong linkage disequilibrium (LD), further functional studies are needed to confirm which is the true genetic variant. What is clear is that a major genetic risk factor for AMD occurs at this 10q26 locus with an up to 10 fold increased risk of developing AMD (150).

Variation in another genetic region coding for complement components has been associated with AMD, and as for 10q26, debate is ongoing as to the precise source of the association. The region is 6p21 where the C2/CFB gene complex resides, although in this case variation is protective for AMD. For example factor B activates the complement system; it is known that a snp in this gene associated with protection from AMD (rs641153) reduces the gene product's function, hence perhaps reducing overall complement activity. However as the C2/CFB region is one of high LD, uncertainty exists as to the precise source of the association between the region and AMD.

Variation in C3 has been shown to increase the risk of developing AMD particularly in Caucasians (152). In addition there is a protective deletion of CFHR1 and CFHR3 occurring close to the CFH locus in 8 % of AMD patients (153) Furthermore a pooled analysis of 21460 participants found the ε4 allele of APOE to be associated with increased risk of AMD (154), although prior studies have stated that given the allele's association with cardiovascular disease, the possibility of a survivor effect underlying this association should be considered. Understanding regarding the contribution of other genetic loci containing genes such as SERPING1, CFI, TIMP3 and TLR3, and genes associated with lipid

metabolism (other than APOE), as well as the role of intronic sequences, mitochondrial DNA and gene-environment interactions is evolving.

AMD is unusual among common diseases (such as diabetes, breast cancer etc) in that a relatively small number of genes of large effect have been identified. The benefit in clinical practice in the UK of such genetic knowledge has yet to be realised. For example the utility of commercially available genetic testing kits for estimated risk of developing AMD is uncertain. However several potential benefits of AMD genetics are likely to emerge.

Firstly individualised advice may be possible in future. Next generation sequencing and novel statistical approaches may facilitate the identification of genetic loci associated with particular subtypes of AMD. For example the ARMS2/HTRA1 locus has been shown to influence the subtype of neovascular lesion in AMD (155). New techniques will also facilitate testing for genetic changes of low prevalence in the population but of particular significance for individuals or families. The overall result of new technologies may be more accurate phenotyping with genetic correlation, and advice on prognosis.

Secondly resources for advice regarding lifestyle factors could be focused, as it is known for example that if patients carry a specific genetic risk factor at 10q26, the association of AMD and smoking is approximately three times stronger (156).

Thirdly knowledge of the genetic basis of AMD may inform the development of novel therapeutic approaches. For example complement inhibitors have been the subject of several phase two trials, although there is no evidence to justify their use at present.

Finally an individual's response to treatment may be influenced by their genetic status, which would potentially allow creation of a biomarker profile to help guide treatment. It has been shown for example that patients carrying the CFH Y402H CC genotype have been to shown to develop greater visual acuity loss after photodynamic therapy (PDT) (157). In addition patients with the CFH Y402H CC genotype fared significantly worse after intravitreal Bevacizumab injections than did those with the CFH TC or TT genotypes (158).

6.5 Others

6.5.1 Cataract Surgery and Macular Degeneration

The relationship between cataract surgery and the subsequent development of age-related macular degeneration (AMD) is controversial (159-167). It is thought that both AMD and cataract result from accumulation of oxidative damage in the form of reactive oxygen species, from both internal sources (mitochondria) and external sources (sunlight) (168). There are also reports in the literature showing an increased risk of AMD following cataract surgery. A meta-analysis (23) found that cataract surgery was associated with late AMD with an risk ratio from pooled prospective studies of 3.05 (95% confidence intervals 2.05 - 4.55). The Beaver Dam Eye Study was included in that meta-analysis, but has since published 15 year results (165), finding that cataract surgery is associated with increased AMD risk, after correcting for other risk factors including CFH and ARMS2 risk alleles. The risk was greatest if surgery had been performed more than five years previously rather than less than five years from the study time-point.

A Cochrane review on the subject of whether cataract surgery is harmful or beneficial in patients with AMD found insufficient evidence from prospective randomised trials to draw a conclusion, though acknowledges there may be ethical issues in delaying cataract surgery as part of a trial (169). Retrospective studies have shown that patients with a mild to moderate degree of AMD and moderate / severe cataract will benefit from surgery (161, 162). It is prudent to warn patients that the visual prognosis is guarded if signs of AMD are present in the macula. However cataract surgery can produce long lasting visual benefits in patients with AMD (170).

As the relationship between cataract and surgery for cataract with AMD is unclear, additional long terms observational cohort studies are required. The use of OCT prior to and following surgery may be useful to rule out any subtle pre-existing neovascularisation that may be difficult to pick up in cataractous eyes.

6.5.2 Sunlight Exposure and Macular Degeneration

The relationship between sunlight exposure and macular degeneration is not clear cut (171). Different wavelengths of light can penetrate the eye to different degrees with UV radiation mainly being absorbed or deflected by the lens and cornea. There is laboratory evidence that exposure of the macula to blue wavelengths of light can lead to changes similar to macular degeneration (172). There is also evidence to suggest that high levels of pigment in the form of lutein and zeaxanthin which absorb blue light has a protective effect on the development of macular degeneration but translating this information into clinical studies is more difficult (49). The European Eye Study recruited subjects from seven centres, chosen at least partly to give a large range of latitudes: 4753 subjects were studied. In the study blue light exposure, estimated from questionnaires and metereological data, was significantly associated with increased risk of AMD in those with the lowest blood levels of combined anti-oxidants (173).

The best way to accurately estimate total light exposure would be in the form of a prospective cohort based study but this is not possible given the length of time patients would be required to be followed up. Cross- sectional and population based studies have lead to inconsistent findings in terms of the relationship between light exposure and the subsequent development of AMD (42, 45, 174). Despite conflicting results it would seem prudent to advise sunglasses with 100% protection against UVA and UVB radiation in bright environments. Sunglasses provide roughly 50% more UV-blue photoprotection than either violet or blue blocking intraocular lenses (175). More information/evidence for a protective effect of blue filtering lenses in the context of early AMD, and development of AMD is required.

6.5.3 Gender/sex hormones

A meta-analysis found that AMD was not associated with gender (23). Previous studies have reported a higher prevalence of AMD in women, but much of this increased risk can be attributed to increased longevity (176). Conversely, the

association between vascular disease and AMD has lead to the hypothesis that exposure to oestrogen (either endogenous or exogenous) might lead to a reduced risk of AMD in women.

Markers of exposure to oestrogen in women, such as age at menarche and menopause and use of hormone replacement therapy are inconsistently associated with AMD (174, 177-185). In one randomised controlled trial (186) the Women's Health Initiative study randomised women to conjugated equine oestrogens (CEE), CEE with progestin (CEE+P) or to placebo. Over 4,000 women aged 65 years and above in this trial were evaluated for the presence of AMD after an average of 5 years treatment. Overall there was no association between oestrogen supplementation and development of AMD. The group treated with CEE+P had a reduced risk of one early sign (soft drusen) and also of neovascular AMD however the study was underpowered and the authors were unable to make a definitive statement regarding these effects.

6.5.4 Race

A meta-analysis (23) found the odds ratio of AMD was not significantly different for whites compared with other races/ethnicities in two prospective cohort studies (odds ratio 0.91, 95% confidence intervals 0.49 - 1.69) or in two cross-sectional studies (1.09, 0.09 -13.56). However individual studies have detected associations. There is a higher prevalence of large drusen, pigmentary abnormalities, neovascular AMD and geographic atrophy in white people compared with black people (124, 187-190). Some studies have reported a lower prevalence of AMD in Hispanic people (85, 191, 192) but similar prevalence of early signs of the disease (85, 191).

6.5.5 Educational status/social class

A number of studies have suggested that increasing years of education are associated with a decreased risk of AMD (85, 183, 191). However strong trends

were not observed in these studies and several studies have found no association (193, 194). It is unlikely that socioeconomic status is an important factor determining the distribution of AMD in the population.

Practical Points

Smoking is the most consistent risk factor for the development of late AMD. Patients should be given advice on cessation of smoking.

As the largest trials (AREDS 1 and 2) were conducted in well nourished populations, the evidence for nutrient supplementation in prevention of progression from early to late AMD remains unproven.

The AREDS formulation which contains beta- carotene has been associated with an increased risk of lung cancer in smokers. If patients wish to use antioxidant supplementation they should be made aware of these risks.

7. Natural history of vision loss

The onset of GA or CNV results in progressive and unremitting loss of central vision in the affected eye. A number of studies have shown that extrafoveal CNV will grow towards the fovea. Once foveal involvement has occurred CNV will expand and involve ever increasing areas of the macular retina. Thus the majority of eyes will experience moderate (defined as a doubling of the visual angle which equates to a 3 line worsening on the ETDRS visual acuity chart) or severe vision loss (defined as a quadrupling of the visual angle and which equates to a 6 line worsening on the ETDRS chart).

7.1 Natural history of visual acuity outcomes without treatment

Eyes with only drusen typically do not suffer overt vision loss. Occasionally such eyes may manifest subtle changes in visual function but mostly patients are unaware of any change. Distortion can be reported by patients with large soft

drusen with related focal pigment epithelial detachments and patients with geographic atrophy, although much more commonly in patients with exudative AMD. Many investigators have shown subtle changes in acuity, contrast sensitivity, colour vision, dark adaptation and scotopic sensitivity in eyes with early features of AMD (195-197).

GA is associated with severe central visual decline. A longitudinal study of GA found that 31 % suffered a 3-line loss in acuity within 2 years of diagnosis and that this had increased to 53% at four years (198, 199). Once neovascularisation has occurred, the natural history is one of acute central visual disturbance followed by unremitting vision loss (200, 201). Over a period of time which is generally variable, relative scotomata become absolute. Some patients with a fellow eye with good vision will not notice any such changes despite the onset of neovascularisation (202). Guyer et al reported the visual acuity loss associated with subfoveal CNV and an initial visual acuity of 20/100 (6/30, 0.7logMAR) or better, 77% had lost 4 lines of vision by 24 months and 64% 6 lines. They also reported that increased size of CNV at baseline is associated with a decreased initial visual acuity (201).

In the Macular Photocoagulation Study randomised controlled trials for laser photocoagulation the primary outcome was distance visual acuity. The natural history of untreated eyes from the control groups of these trials shows a massive loss of vision. The trials investigated extrafoveal, juxtafoveal and subfoveal membranes. In the subfoveal new CNV study, 1.9 lines of vision were lost in the first three months, 4.4 lines at 24 months and 5.5 lines at 48 months (203, 204). In the subfoveal recurrent CNV study 1.7 lines were lost from baseline to 3 months, 3.4 lines from baseline to 24 months and 3.9 lines after 36 months (205, 206).

Table 1 (below) shows the proportion of eyes in each group to experience severe visual loss (≥6 lines) from baseline to each subsequent visit (204, 207, 208). The proportions are relatively similar for each location of CNV studied.

Study (Number at Baseline)	3 M	6 M	12 M	24 M	36 M	48 M
Extrafoveal (N=117)	0.10	0.29	0.41	0.56	0.63	0.65
Juxtafoveal (N=249)	0.13	0.28	0.45	0.54	0.61	0.63
Subfoveal recurrent (N=114)	0.11	0.19	0.29	0.38	0.39	
Subfoveal new (N=183)	0.11	0.18	0.30	0.39	0.38	0.45

Table 1: The proportion of eyes losing at least 6 lines of vision distance visual acuity (DVA) from baseline to each follow up visit in the observational groups of the MPS clinical trials

Mean visual acuity of the placebo group in the Treatment of AMD with Photodynamic Therapy (TAP) study was 20/80 (0.6 logMAR) at baseline. By 3 months this had reduced to 20/126 (0.8 logMAR) and by 12 months to 20/200 (1.0 logMAR). Mean visual acuity was 20/200 at 24-month follow up as well (209, 210). In the Verteporfin In Photodynamic Therapy (VIP) study, mean baseline visual acuity was 20/100 (0.7 logMAR). By 12 months, mean acuity had reduced to 20/126 (0.8 logMAR) and at 24 months reduction to 20/200 (1.0 logMAR) had occurred (210).

The most robust information on natural history comes from interventional controlled clinical trials which have included a placebo or control arm. A recent meta-analysis of data on 4362 participants in high quality studies found there was a steady decrease in visual acuity (211). The mean VA change in logMAR progressed from 0.1(1 line lost) at 3 months to 0.3 (2.7 lines lost) after 12 months and 0.4 (4 lines lost) after 24 months. The proportion of patients who developed severe vision loss (>6 lines) from baseline increased from 21.3% at 6 months to

41.9% by 3 years. The proportion of patients with VA worse than logMAR 1.0 (20/200 Snellen) increased from 19.7% at baseline to 75.7% by 3 years.
The Seven Year Update of Macular Degeneration Patients (SEVEN UP) was a study of a convenience sample of 65 participants who had completed MARINA or ANCHOR, as well as HORIZON (an open-label two year extension of MARINA and ANCHOR) (212). A mean of 7.3 years had elapsed since entry to MARINA or ANCHOR, and ranibizumab had been given on an as needed basis since those trials. While the mean BCVA change was -8.6 letters, 37% had a BCVA of 20/70 or better, with a trend towards better outcomes with more injections.

7.2 Lesion morphology and vision loss

While a number of studies have examined the visual function of eyes with early AMD, the relationships between visual function and more advanced AMD lesions have not been systematically investigated (195, 196, 213). The treatment and control groups of clinical trials such as the MPS have shown that a wide range of visual function is possible. It has been shown that a large number of eyes with large lesions have good visual acuity and that some with small lesions have poor visual acuity (214). AMD does not appear to be a single cohesive morphological entity and therefore it is not surprising that there is inconsistency between the severity of retinal changes and visual function (214, 215). Various macular lesion characteristics have been shown to influence vision. These include in the first instance the nature of pathology, where the exudative stages have been shown to cause much more loss of visual acuity as compared to those with, atrophic stages (216). Secondly the location of the lesion, patients with subfoveal lesions and those with posterior edges extending towards the fovea tending to have poorer vision (200, 217). Finally the extent of the lesion and the components of the lesion influence vision, where subretinal scars result in worse acuity than lesions without fibrosis (198, 200). A study by Hogg et al has also shown that fibrosis, when present within the fovea, results in notably worse visual acuity when compared with fibrosis at an extrafoveal location (218). The extent of lesion or lesion components were also found to affect vision, with larger areas of

atrophy and fibrosis adversely influencing clinical measures of vision. Blood and exudate also had an adverse effect on vision but to a lesser extent. Lesions exhibiting pigmentation, subretinal fluid and CNV were found to have acuity that was no worse than lesions without these components (218).
In a study of 93 patients with subfoveal CNV, the status of the better or worse seeing eye was found to influence visual acuity (219). In better seeing eyes, the correlation between the classic component and contrast sensitivity was significant and in worse seeing eyes, the total lesion size was significantly correlated with resolution and contrast. The distance between the fovea and healthy retina was also significant for predicting visual function.

Practical Points

If left untreated CNV will progress to involve the foveal avascular zone in the majority of eyes leading to moderate or severe visual loss.

7.3 Contrast Sensitivity

Limitations associated with the assessment of conventional high contrast visual acuity measurements have been highlighted for over 40 years (220).
These limitations hinge on the fact that much of what we require our visual system to do involves the identification of detail within a low contrast world, as opposed to the assessment of spatial resolution under conditions of very high contrast . Traditionally, and within the laboratory setting, contrast sensitivity has been measured using computer generated sinusoidal grating patterns on high quality oscilloscopes (220). Testing, using psychophysical techniques of this nature, may be challenging (221), being potentially expensive, time consuming and impractical within the busy clinical setting. Paper or “hard copy” screening tests designed using sinusoidal gratings were subsequently developed and, of these, the most well known are the Cambridge Low Contrast Grating Cards (222), Arden Gratings (223) and the Vistech (VCTS) Charts (224). None of these tests have been used extensively within (NHS) clinical settings, one reason being

that clinicians would appear to have an inherent preference for tests incorporating optotypes.

Of the clinical tests which have subsequently been developed to help overcome this problem, the most widely known is the Pelli-Robson chart. This test, which is essentially now recognised as the “gold standard” against which other optotype based CS tests are judged, utilises triplets of letters decreasing in contrast by a factor of $1/\sqrt{2}$ from top to bottom. Before inclusion in clinical trials its test-retest reliability in AMD should be borne in mind (225). Alternative optotype based charts are the “MARS letter contrast sensitivity chart”, on which successive letters decrease in contrast by 0.04 Log Units (226), and a series of charts, produced to mimic high contrast logarithmically designed acuity charts but on which letters are printed at designated low contrast values. These charts include the “Ragen Low Contrast Letter Charts” (227), the “Bailey Lovie Reduced Contrast Chart” (228) and the “Lea Low Contrast Symbol Charts”.

Comparison of data acquired using different tests is difficult and often inappropriate as the design principles differ. Tests such as the Pelli-Robson assesses contrast sensitivity at a single spatial frequency near the peak of the CS curve whereas those like the Bailey-Lovie chart test acuity or spatial resolution at a specified level of reduced contrast .

There is, however, considerable evidence to suggest that reduction in contrast sensitivity and low contrast acuity can be a predictor of impaired performance, particularly in relation to those tasks that involve driving (229), mobility (230, 231), postural stability (232), face recognition (233) and reading speed (234, 235).

In the US, the National Research Council now recommended in 2002 that CS be used as a basis for disability determination on the Social Security Programme.

In studies on ageing, visual acuity has been found to have deteriorated by a factor of 2.4 times in those over the age of 90 years, compared to that of younger observers in their 50s. The deterioration of low contrast acuity, in the presence of glare, has however been shown to decrease by a factor of 18 times (236).

Significant deterioration of low contrast acuity has, in addition, been shown to begin to deteriorate approximately 12 years earlier than high contrast acuity. Against this background, it has been suggested that low contrast acuity measures could be predictors of subsequent high contrast acuity loss (237). Most studies do, however, show a moderate correlation between measures of VA and contrast sensitivity with Rubin et al suggesting that a 6 letter loss of CS on the Pelli Robson chart has a similar impact on self reported visual disability as a 15 letter loss (3 lines) on a high contrast LogMAR acuity chart (238).

Studies designed to evaluate the impact of AMD on contrast sensitivity and the relationship between CS, VA and functional vision, in this condition, are not easy to interpret. In a study of patients enrolled for radiation therapy of macular neovascular membranes, CS measurements could not be used consistently to predict similar rates of progression (239). Kleiner at al, using Ragen Letter Charts, found that when comparing CS in a group of patients (n=15) with macular drusen to that from a group of age matched norms (n=27) all with an acuity of at least 20/20, those with drusen showed a greater reduction in the number of letters read as target contrast decreased (240). Stangos et al found that the CS loss in eyes with drusen was most significant at mid and high spatial frequencies (241). Alexander et al, although finding a significant correlation between CS loss and decreased VA in a range of patients with early to late AMD, noted that there was considerable disparity at all acuity levels (242). In a study involving 209 patients with either unilateral or bilateral AMD, Bansback et al found CS to be a significant independent predictor of health related QOL and health utility (243).

Attempts to correlate the composition and location of macular lesions in cases of choroidal neovascularisation have shown that the strongest correlation is between lesion size and CS (r=0.52) and that the relationship is strongest when the lesion was predominantly classic (219). Results recorded under conditions of varying luminance have also been reviewed, the conclusion being that adaptation systems which enable patients to detect both high and low contrast detail are impacted by AMD (244). Suness et al have, in particular, shown low luminance

deficit (LLD) to be a strong predictor of subsequent VA loss in a cohort of 91 patients with geographic atrophy, followed over a 2 year period (245).

7.4 Near Vision and Reading Speed

In addition to acuity and contrast other tests of macular function include near acuity and reading speed (246). Threshold near acuity is determined first and then reading speed (number of words read per minute is recorded either at the threshold acuity or using words just larger than reading speed) (246, 247). The Macular Photocoagulation Study was the first clinical trial to use reading speed as an outcome measure (204). Since then very few studies have used near acuity and reading speed (247, 248) as an outcome measure. This is probably because these tests take considerable length of time to undertake. Although distance VA remains the most popular outcome measure, recent work on health related quality of life shows that near acuity and reading speed exhibit correlations with self reported visual functioning that are not explained by visual acuity alone (249).

7.5 Self reported visual functioning and quality of life

The term “quality-of-life” (QoL) is used to represent several distinct concepts. These include physical functioning (health status), functional status (ability to participate in daily activities) social functioning (interactions and relationships) and psychological functioning (satisfaction and well-being). In addition, QoL can be evaluated with generic scales or disease-specific questionnaires. It is widely agreed that vision-specific instruments provide more sensitive measures of the impact of AMD on QoL.

Several comprehensive reviews of QoL instruments have been published since 2000 (250-254). Of the 25+ vision-specific QoL instruments, only three were specifically developed to assess patients with AMD (the MacDQoL, DLTV, and MLVQ). However several of the other popular questionnaires have been validated in patients with AMD (VF-14, ADVS, NEI-VFQ) or in low vision patients, most of whom had AMD (MAI, VQoL). Validation of QoL questionnaires for AMD

has mostly followed the traditional methodology which includes principal components analysis and measures of internal consistency reliability to reveal the underlying dimensionality of the instrument, and correlation with clinical vision tests (e.g. acuity or contrast sensitivity) as an indicator of construct validity. A shift towards the use of item-response theory has occurred, in particular Rasch analysis, to validate questionnaires (255). Rasch analysis offers several distinct advantages over the traditional approach (256): ordinal measures are converted into a linear interval scale which is more amenable to conventional parametric statistics, missing responses are easily accommodated, the questionnaire can be efficiently targeted to the functional level of the patient sample, and data can be compared across different questionnaires (257).

There is insufficient space for a comprehensive review of QoL outcomes in AMD. Instead, we highlight some of the key findings, emphasising treatment studies that included a control group. Few vision-specific instruments attempt to measure the full spectrum of QoL, with the possible exception of the MacDQoL. The greatest emphasis in studies to date has been on physical function – the ability to participate in visually demanding activities such as reading the newspaper or recognizing a face from across the room.

Vision-related quality of life has been shown to decline significantly as early AMD progresses to late AMD over a 15 year follow-up (258). Neither the Macular Photocoagulation study nor the Photodynamic Therapy study reported QoL outcome data. The Sub Macular Surgery Trial failed to show any difference between treatment and controls using the NEI-VFQ (259) as did the Sub-Foveal Radiotherapy Study, using the DLTV (260). Anti-VEGF treatments including ranibizumab (Lucentis) (261) and pegaptanib sodium (Macugen) (262) both showed significant improvements in QoL measured with the NEI-VFQ. The provision of low vision services improved functional ability in a non-controlled study despite deterioration in vision (263). A self-management training course improved self-efficacy compared to waiting list controls (264). Not all the variation in vision-related quality of life in AMD is explained by VA (265)(266). For

example taking into consideration AMD occurs in the ageing population, it should be noted that cognitive abilities also play a role (267).
One controversial issue in the assessment of QoL is the determination of utility values. Utility values measure the desirability of health states and are used in economic analysis of cost-effectiveness of various treatment options.
Considerable work has been done to develop reliable methods for assessing utility values based on patient preferences. The most common method – the time tradeoff (TTO) – determines how many years of remaining life expectancy a patient would trade in return for a guarantee of perfect health (vision). TTO utilities have been linked to visual acuity in the better eye (268). In fact, most of the evaluations of cost-effectiveness of treatments for AMD have been based solely on better eye acuity. However, it has been shown that acuity in the worse eye also influences QoL (269). Moreover, other dimensions of visual function – such as contrast sensitivity and visual fields – independently affect QoL. In one study of patients with AMD, contrast sensitivity had the dominant effect (243). Finally, other methods based on patient preferences, such as conjoint analysis (270) do not yield utility values that are equivalent to TTO, nor are they as closely related to visual acuity.

8. Therapies for acute neovascular AMD

This section is concerned with the evidence for past, current and emerging therapies for choroidal neovascularisation (CNV) secondary to AMD, which is an area of rapid development. It will mainly concentrate upon current therapies and evidence that has been published in peer-reviewed journals.

8.1 Laser photocoagulation

The Macular Photocoagulation Study (MPS) Group undertook a series of randomised, controlled trials assessing photocoagulation treatment for CNV.
The object of the treatment was to destroy the neovascular complex with heavy

confluent laser, and thereby try to reduce further loss of vision resulting from its further enlargement and/or ongoing leakage. Lesions were classified as extrafoveal if 200μm or more from centre of the foveal avascular zone (FAZ), juxtafoveal if they were 1-199μm from the centre of the FAZ, or subfoveal.

8.1.1 Extrafoveal lesions

This MPS trial was carried out using argon laser before the differentiation of angiographic patterns into classic or occult was recognised. Well-defined extrafoveal lesions were included with a baseline vision of 20/200 or better. Lesions were treated with heavy confluent laser, with 100μm margin beyond the lesion resulting in an absolute scotoma within the area of treatment. At 5 year follow-up, 64% of untreated vs. 46% of treated eyes had progressed to severe visual loss. Recurrences were common, and were seen in 54% of treated eyes at 5 year follow-up (207). Another prospective clinical trial in the UK reached similar conclusions (271).

8.1.2 Juxtafoveal lesions

In this MPS trial krypton laser was used for lesions that were up to 199μm from the centre of the FAZ, or CNV 200μm or further from the FAZ with blood or blocked fluorescence extending within 200μm of the centre of the FAZ (272). Lesions were treated with 100μm margin, or 100μm into the blood or until the centre of the FAZ. At 3 year follow-up 49% of treated eyes compared to 58% untreated eyes had lost six or more lines of visual acuity. Most of the visual loss in both groups occurred within the first few months after randomisation. In addition, more than twice as many treated patients as untreated patients retained visual acuity of 20/40 or better. Persistent CNV, defined as leakage detected during the first 6 weeks after laser treatment, was present in 32% of eyes compared to only 10% in the extrafoveal argon study. There was a 50% recurrence rate at 2 year follow-up (273, 274).

8.1.3 Subfoveal lesions

Two MPS trials were undertaken to assess the effectiveness of laser treatment in eyes with subfoveal CNV (204). One trial evaluated the effectiveness of laser photocoagulation of subfoveal lesions without previous treatment, in which there was a component of classic and the whole lesion was well-demarcated. Baseline vision was between 20/40 and 20/320 and the lesions included in the trial were no larger than 3.5 disc areas in size. There was an initial reduction of vision of approximately 3 lines, but by 2 years the vision had dropped more than 6 lines in 37% of untreated vs. 20% of treated eyes. By 4 year follow-up 30% of treated eyes vs. 60% of untreated eyes were 20/400 or worse. Eyes with smaller lesions and poorer acuity seemed to benefit most from treatment. A second trial evaluated results of treating recurrent extra/juxtafoveal lesions with subfoveal extension and also showed significant benefit compared to no treatment.

Practical Points

Laser treatment can no longer be justified for most cases of neovascular AMD, having been superseded by treatment with anti-VEGF agents. Laser photocoagulation might still be considered for lesions well away from the fovea thereby avoiding the time investment, risks and cost associated with anti-VEGF agents (275).

If laser treatment is given patients should be warned that they may be aware of a permanent scotoma in their vision following treatment. Patients should be examined two weeks and 6 weeks following laser (with fluorescein angiography) to confirm that the CNV has been ablated, and thereafter depending on clinical findings.

8.2 Photodynamic therapy with Verteporfin

This is a procedure whereby the photosensitising dye Verteporfin (Visudyne, Novartis) is given intravenously. Verteporfin binds to LDL in the circulation and it is then relatively selectively taken up by rapidly proliferating endothelial cells

which have high LDL receptor expression. This is followed by the delivery of laser light of a wavelength of 689nm to the CNV lesion as a single spot with a diameter 1000μm larger than the greatest linear diameter of the lesion. The energy from the laser is taken up by the Verteporfin, and this leads to damage to proliferating vascular endothelial cells and thrombotic occlusion of the blood vessels within the CNV lesion. The major advantage of this approach over laser photocoagulation is that there is minimal damage to the overlying retina (276, 277).

The FOCUS trial of 164 patients compared PDT alone with PDT plus ranibizumab (278). Participants with predominantly classic CNVM were randomised in a 2:1 fashion to receive PDT followed by intravitreal ranibizumab 0.5mg and then monthly ranibizumab or PDT followed by sham injection monthly for 23 months. PDT was performed quarterly in both groups as needed. The study met its primary efficacy endpoint of maintaining or improving vision (defined as a loss of less than 15 letters in visual acuity on ETDRS chart). Results at 12 months showed that over 90 percent of patients (95/105) treated with the combination of PDT and ranibizumab maintained or improved vision compared to approximately 68 percent (38/56) treated with PDT alone ($p<0.0003$). This study raised safety concerns over the combination of PDT and ranibizumab as a higher proportion of uveitis was reported in this group. PDT and Lucentis were initially given 7 days apart. The protocol was later amended such that in the remainder of the study, PDT was administered at least 28 days prior to and no sooner than 21 days after administration of Lucentis. At two years (279) 25% of the combination group and only 7% of the PDT-only group had gained 15 letters or more, and there was a significant difference in the mean BCVA changes with superior results achieved in the combination group than the PDT-alone group. The incidence of endophthalmitis was 2.9% and serious intraocular inflammation 12.4% in the combination group, and 0% in the PDT-alone group. The lyophilized formulation of Lucentis used in this study is different from the one used in monotherapy clinical trials like MARINA and ANCHOR.

In the 'EVEREST' study vPDT produced superior visual outcomes for polypoidal choroidopathy either alone or in combination with ranibizumab, than ranibizumab alone (280).

Practical Points

vPDT is no longer justified as monotherapy for nvAMD.

PDT is recommended only in patients with idiopathic polypoidal choroidopathy. It is recommended that it is performed within 1-2 weeks of fluorescein angiogram and then as required 3 monthly.

Severe vision loss can occur immediately after treatment in 1-4% of patients and this may be permanent in a small proportion of cases.

Idiosyncratic back pain occurs in 1-2% of patients which resolves when the infusion is stopped.

Patients should be advised to avoid direct sunlight exposure for 2 days following treatment.

Steroids

Steroids have several theoretically beneficial effects in the management of AMD (281). For example they are anti-angiogenic, anti-fibrotic, down-regulate inflammation and stabilise the blood retinal barrier.

A Cochrane review identified three trials on intravitreal steroids for neovascular AMD, but found the evidence was of variable quality, and did not support the use of steroids (282).

8.5.2 Anecortave acetate

Anecortave acetate (Alcon) is an angiostatic cortisone, but it does not have the ocular complications of many steroids including raised intraocular pressure and cataract. It is administered at an interval of every 6 months by posterior juxtascleral delivery.

Promising results were seen in a phase II study at 12 months (283). In this study of predominantly classic lesions when 15 mg of Anecortave acetate was administered at an interval of every 6 months 79% of patients lost less than three lines of vision compared to 53% in the sham-treated group (p=0.0323). However, there were some concerns about this study because of a high rate of loss of participants.

A phase III prospective, masked, randomised noninferiority clinical trial was performed comparing Anecortave acetate (15 mg) every 6 months with Verteporfin PDT given every 3 months if there was angiographic leakage for predominantly classic CNV (284). At 12 months with 45% of Anecortave treated eyes lost fewer than three lines of vision compared to 49% of PDT treated eyes with no statistically significant difference between the groups (p=0.43). During the study it became apparent that reflux of the Anecortave acetate after delivery was a problem and a subgroup analysis of patients in whom this was controlled gave a more favourable outcome. No safety problems with Anecortave acetate were detected. The drug is not licenced for use within Europe although it is licensed in Australia.

Studies to assess juxtafoveal anecortave in preventing progression of dry to neovascular AMD (clinicaltrials.gov identifier: NCT00332657) and to assess its efficacy and safety.for subfoveal neovascular AMD (NCT00065728) were both terminated, each due to a "management decision", speculatively because anti-VEGF agents have come to dominate treatment. It has been suggested, based upon a small retrospective case series, that anecorvate may have a role in treating leakage at the edge of fibrotic lesions (285).

8.2.1 Combined Verteporfin PDT and triamcinolone

Several small studies have shown that Verteporfin PDT combined with intravitreal triamcinolone acetate (IVTA) may improve the outcome of standard verteporfin PDT, and reduce the number of retreatments (286-293). The Verteporfin Intravitreal Triamcinalone Acetonide Study (VERITAS) trial which looked at PDT together with either intravitreal injections of Macugen (n= 38) or 1mg (n= 32) or 4mg of triamcinalone (n=41) was stopped after 6 months of follow-up as there were no significant difference between groups in terms of loss of 15 letters on the visual acuity test which was the planned primary endpoint of the study (unpublished data presented at ARVO 2007). Any potential benefits of intravitreal triamcinalone must be weighed against the potential complications of treatment that include cataract progression, increased intraocular pressure and the risk of endophthalmitis per injection (294, 295). Triamcinolone used alone has not shown to be effective in the long-term, and the role of intravitreal triamcinolone in the management of AMD, if any, is yet to be established (296). Combination therapy of PDT verteporfin and periocular triamcinolone injection may be safer but clinical trial evidence of the efficacy is limited and a randomized controlled trial did not find any reduction in the fluorescein leakage 3 months after a single periocular injection of corticosteroid and PDT compared to PDT alone (297).

Practical Points

Evidence does not support the use of periocular anecorvate acetate or intravitreal triamcinolone for nvAMD, alone or with vPDT. Any potential role of triamcinolone as an adjunct of anti-VEGF therapy has yet to be established.

8.3 Surgery

A Cochrane review found two studies comparing submacular surgery with observation for subfoveal nvAMD. There was no evidence of benefit for surgery in terms of prevention of visual loss, and a significantly increased risk of cataract and retinal detachment following surgery (298). In a subgroup of one of these trials, the submacular surgery trial, surgical removal of CNV was compared with observation for subfoveal CNV that were at least 50% blood and > 3.5 disc areas in size with vision 20/100 or worse. Surgery did not increase the chance of stable or improved visual acuity, and was associated with a high risk of rhegmatogenous retinal detachment, but did reduce the risk of severe vision loss in comparison with observation (299).

There are several case series reporting results of pneumatic displacement of submacular haemorrhage with or without tissue plasminogen activator (tPA), but visual outcomes have been poor due to the underlying CNV (300-304) (305). However clinical trials are required to investigate the optimum management of submacular haemorrhages in AMD (306). It remains to be seen whether this approach combined with intravitreal anti-VEGF treatment would give improved results.

Macular translocation has been shown to significantly improve vision in a proportion of treated cases (248, 307-311) with 25% of a cohort of 40 patients undergoing surgery maintaining a three line gain at three years follow-up (312). NICE assessed the evidence for macular translocation in 2004 and reported that 'the current safety and efficacy data would not support its use without special arrangements for consent, audit and research' (http://www.nice.org.uk/nicemedia/pdf/IPG048guidance.pdf) and in 2010 reiterated this advice (IPG340) on the basis that evidence suggested that macular translocation was efficacious in only a proportion of patients with nvAMD, and that there was the potential for serious adverse events. A Cochrane review (313) on macular translocation for neovascular AMD identified only one randomised study. The study had 50 participants with predominantly classic subfoveal CNV, randomised to macular translocation surgery or vPDT.

Participants, the surgeon and visual acuity assessors were unmasked. The results did not reliably demonstrate the usefulness of translocation surgery for nvAMD, and highlighted the potential for serious complications such as retinal detachment.

8.4 Ionising radiation

Radiotherapy can inactivate rapidly proliferating cells, and therefore could be of potential benefit in nvAMD by its effect on the capillary endothelium of the CNV. It can be delivered from a source external to the body (teletherapy) or locally (brachytherapy) (314). There have been a number of studies assessing radiotherapy for AMD, and some of these have shown a significant benefit from treatment (247, 315-321).

NICE assessed the evidence for its use in 2004, reporting that there was little evidence for efficacy overall and recommended its use only within clinical trials. (http://www.nice.org.uk/nicemedia/pdf/IPG049guidance.pdf- radiotherapy guidance), and in January 2011 decided not to update the guidance as radiotherapy had been superseded by anti-VEGF agents. The RCOphth guidelines from 2009 (section 8.4) and the Cochrane review in 2010 reported no good evidence of benefit from radiotherapy (322). The 'I-Ray plus aNti-VEGF TREatment for Patients wIth Wet AMD' study (INTREPID) investigated a single dose of external beam stereotactic radiotherapy for patients with nvAMD requiring ongoing injections of anti-VEGF treatments (323). At one year treatment with radiotherapy reduced the number of injections needed, with a favourable safety profile (see section 8.6.3).

Practical points for surgery and radiotherapy

Submacular surgery, macular translocation or radiation monotherapy are not recommended for the management of nvAMD.

8.5 Anti-angiogenic therapy

VEGF-A is a pro-angiogenic growth factor that also stimulates vascular permeability and has a major role in the pathology of choroidal neovascularisation. It exists in a number of different isoforms that result from alternative splicing of VEGF-A mRNA.

8.5.1 Pegaptanib sodium

Pegaptanib sodium (Macugen, Eyetech/Pfizer) binds and blocks the activity of isoforms of vascular endothelial growth factor-A (VEGF-A) that contain at least 165 amino acids. In the VISION study Pegaptanib sodium was given by intravitreal injection at six weekly intervals over two years at doses of 0.3, 1.0 and 3 mg (324, 325). All lesion types were included but patients with predominantly classic lesions received adjuvant PDT treatment making the results difficult to compare with other monotherapies. The recommended dosage is 0.3 mg as the higher doses in the trial did not show additional benefit. After one year a treatment benefit was seen with all lesion types compared with sham with 70% of treated patients lost less than 15 letters of vision compared to 55% controls ($P<0.001$). The risk of severe visual loss (loss of 30 letters or more) was 22% in the placebo group and 10% in the treated group. The response was not dependent upon lesion type with treated patients losing on average between 6-9 letters of vision irrespective of whether predominantly classic, minimally classic or occult and sham treated controls losing between 13-18 letters. The main side effects that occurred were endophthalmitis (1.3% of patients), traumatic lens injury (0.7%) and retinal detachment (0.6%). Following a modification in the protocol, the per-injection rates of endophthalmitis were reduced in year 2 of the study. No systemic side-effects were observed. A further analysis explored visual outcomes in more detail, and suggested that earlier lesions may have improved outcomes, but these results need to be interpreted with caution since this was a secondary subgroup analysis of a relatively small number (64) of patients (326).
Macugen is licensed in the UK for the treatment of CNV secondary to AMD.
The LEVEL study investigated the use of Macugen as maintenance therapy (327). It was a prospective open-label and uncontrolled study which followed 487

patients with neovascular AMD who shown clinical and/or anatomical improvement with one, two or three induction treatments of various types, most commonly with ranibizumab or bevacizumab. For 54 weeks participants received 6-weekly Macugen, plus 'booster treatments', of any agent, as needed. Acuity gains of the induction phase (mean 65.5 letters) were on average maintained to 54 weeks (mean gain 61.8 letters), with approximately half of patients requiring booster treatments, and half of those requiring only one booster. It was suggested that this approach may have benefits for patients with cardiovascular risk factors who require long-term treatment for neovascular AMD. However, in practice, Macugen has no role in the management of AMD.

8.5.3 Ranibizumab

Ranibizumab (Lucentis, Genetech Inc/Novartis) is a humanised Fab fragment of a monoclonal antibody that binds to and inhibits the action of all isoforms of VEGF-A. Two randomised, controlled, double-blind studies were published in which ranibizumab was delivered by intravitreal injection on a 4 weekly basis over two years; the MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular Age-related macular degeneration) (328) and ANCHOR (ANti-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularization in AMD) (329) studies. In ANCHOR and MARINA two doses of ranibizumab (0.3 and 0.5 mg) were administered. In both studies follow up was for two years but the primary endpoint was the proportion of patients losing less than 15 letters from baseline visual acuity at 12 months.

In the MARINA study eyes with minimally classic or occult CNV were treated with ranibizumab (0.3 mg or 0.5 mg) at monthly intervals or sham injections. At 12 months 94.5% of the group given 0.3 mg of ranibizumab and 94.6 given 0.5mg had lost fewer than 15 letters of vision, compared to 62.2% in the sham injection group. Visual acuity improved by 15 or more letters in 24.8% of the 0.3 mg group and 33.8% of the 0.5mg group compared to 5% in the sham-injection group. The mean visual acuity improved by 6.5 letters in the 0.3 mg group and 7.2 letters in

the 0.5mg group but dropped by 10.4 letters in the sham-injection group. All these results were highly significant (P<0.001) and were maintained at 24 months.

In the ANCHOR study eyes with predominantly classic CNV were randomised to receive either ranibizumab (0.3 mg or 0.5 mg) with sham PDT treatment or to PDT with sham intravitreal injections. PDT treatments were given at day 0 and then if needed, based on the investigators evaluation. At 12 months 94.3% of the group given 0.3 mg of ranibizumab (and 96.4 % for 0.5mg group) lost fewer than 15 letters of vision, compared to 64.3% in the PDT treated group. Visual acuity improved by 15 or more letters in 35.7% of the 0.3 mg group and 40.3% compared to 5.7% in the PDT treated group. The mean visual acuity improved by 8.5 letters in the 0.3 mg group, 11.3 in 0.5mg group but dropped by 9.5 letters in the PDT treated group. Either dose of ranibizumab produced a highly significant treatment benefit over PDT (P<0.001).The two year results from the ANCHOR study 24 month demonstrated that the visual acuity improvement with 0.3 mg (mean visual acuity improvement 8.1 letter) and 0.5 mg of ranibizumab (mean visual acuity improvement 10.7 letters) was maintained and the results remained superior to those from PDT treatment (330).

In both ANCHOR and MARINA the complication rates were similar with presumed endophthalmitis and serious uveitis occurring in 1-2% of patients. While there were no statistically significant differences between the ranibizumab treated arms and the sham or PDT arm in terms of systemic complications, overall more patients treated with ranibizumab experienced non ocular haemorrhages than those in the sham or PDT treated arms. These studies show that when given on a monthly basis ranibizumab is superior to PDT for predominantly classic lesions and superior to no treatment in minimally classic and occult CNV.

The PIER study evaluated the efficacy and safety of ranibizumab administered monthly for three months and then quarterly in patients with AMD (331). The primary outcome measure was mean visual acuities at 12 months which were 16.3, -1.6 and -0.2 letters for sham, 0.3mg and 0.5 mg groups respectively with

treated arms achieving significantly better acuity than sham treated. At 2 years visual acuity as superior in treated than sham treated arms, but during the second year patients were converted to monthly 0.5 mg ranibizumab and it was concluded that the benefits obtained with quarterly dosing were not as robust as those observed in previous studies with monthly dosing (332). The EXCITE study compared monthly with quarterly ranibizumab and monthly injections were found to be superior (333). At month 12 mean visual acuity patients receiving ranibizumab 0.3 mg monthly on average gained 8.3 letter of vision, those receiving 0.5 mg quarterly gained 4.9 letters and those receiving 0.5 mg 3.8 letters (per-protocol population).

In the PrONTO (Prospective OCT imaging of patients with Neovascular AMD Treated with IntraOcular Lucentis) study ranibizumab was given on an as needed basis after initial stabilisation of the lesion (334). Results from the PrONTO study suggest that less frequent dosage regimes using OCT parameters to dictate treatment may give equally good visual results. In PrONTO an average of 5.6 injections was used during the year in 40 patients. Patients were only reinjected if central retinal thickness increased by 100µm, new haemorrhage appeared or visual acuity dropped by 5 letters associated with recurrent fluid on OCT or conversion to a classic lesion. Visual acuity increased by 9.5 letters, better than that reported in the MARINA study in which the mean change in visual acuity was +7.2 letters and slightly less than the ANCHOR study +11.3 letters. The 2-year follow-up in the PrONTO study was completed by 37 patients (335) and the reinjection criteria were changed the second year to include any qualitative change by OCT imaging that suggested the reaccumulation of fluid in the macula. This included any change in the retinal thickness, height of a PED, or the reappearance of cysts in the retina or subretinal fluid. The average number of treatments per year was five, with an average of 9.9 total injections over the 2 years of the study. A mean improvement in visual acuity score was 10.7 letters, with a mean reduction in central retinal thickness on OCT of 215µm. Baseline vision was maintained by 78% of patients, and improved by 15 letters or more in 43% of patients.

The SUSTAIN study was a single arm study in which 513 treatment naive patients with neovascular AMD received three initial monthly ranibizumab injections, followed by ranibizumab on an as needed basis, according to prespecified criteria (336). Visual acuity gains during the first three months (mean gain 5.8 letters) fell at month six and were then stable, with a mean gain of 3.6 letters at one year and a mean of 2.7 injections given after the induction phase.
The CATT (337) and IVAN (338) studies were compared monthly vs prn treatments using ranibizumab and bevacizumab (i.e. both had 4 arms); the comparisons between the two drugs are discussed in section 8.5.4. In the CATT study the ranibizumab dose was 0.5 mg and patients who received treatments up to monthly based upon clinical and OCT criteria over two years has a mean improvement in visual acuity of 6.7 letters whereas those who had injections every month improved by 7.8 letters. However, half the patients in the monthly treatment arm were switched to the pro re nata schedule in year 2 and in these patients there was a significant 2.2 letter drop in vision.
In the IVAN study patients had monthly injections of ranibizumab of a discontinuous regime. In the discontinuous regime they were treated monthly for three months. After that time they were followed up monthly and if further treatment was indicated based on clinical and OCT findings a further 3 monthly injections were given. After 12 months discontinuous treatment was equivalent to continuous treatment. In summary these two studies together suggest that if monthly injection is superior to prn treatments the differences are not large.
The European Medicines Authority suggesting an approach that is 'patient-centric' treating on as needed basis (339). This approach is more likely to avoid under- or overtreatment, and also make the most efficient use of NHS resources. Less than monthly injections may be adequate for some, but monthly assessment is the gold standard as present knowledge does not allow accurate prediction of which patients are at risk for CNV recurrence.
The 0.5mg dose has been licensed for use in the USA, Europe and UK.

Systemic safety

Intravitreal ranibizumab is generally safe. Concerns remain that there may be a small excess of arteriothrombotic events (ATEs, defined according to the Antiplatelet Trialists' Collaboration group as nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death owing to vascular or unknown causes) compared to controls. This is because of the physiologic roles of VEGF (340). An analysis from the results of 5 landmark trials showed no increased risk of ATEs for 0.5mg ranibizumab compared to controls, except amongst participants at high risk of cerebrovascular accident there was a significantly higher odds ratio (7.7; 95% confidence intervals 1.2-177) of stroke with ranibizumab (341). Ongoing monitoring within trials was recommended.
HORIZON (342) was a two-year open label extension for patients who had completed two years of participation in MARINA, ANCHOR or FOCUS. Intravitreal ranibizumab was given at the investigators discretion, every month at most with review at least three monthly. The proportion of those with ATEs in the groups who had received any ranibizumab was 5.3% (n=790) and 3.2% in those who had received no ranibizumab (n=63) in the first two years.
Placebo arms will not be used in ongoing and future clinical trials on nAMD since the advent of anti-VEGF treatment. When IVAN and CATT data were combined there was a small excess of serious adverse events (SAEs) with bevacizumab compared to ranibizumab, with an odds ratio of 0.75 (95% confidence intervals 0.61 - 0.92). However analysis of the SAEs found the most common system involved was the gastrointestinal, and the incidence of SAEs was greater for those treated with pro re nata bevacizumab compared to the mandatory monthly group. There was no obvious biological rationale for such a finding, thus raising the possibility of a type one statistical error. There was no difference in the incidence of ATEs with one drug compared to the other (see section 8.5.4).

8.5.4 Bevacizumab (Avastin)

Bevacizumab (Genentech Inc.) is a humanised full-length antibody that is derived from the same monoclonal antibody as ranibizumab, therefore it is likely to recognise the same epitope on all isoforms of VEGF as ranibizumab, but bind

with a different affinity. The serum and vitreous half lives of bevacizumab are longer than those of ranibizumab. Bevacizumab was designed for use as a cancer therapeutic and is licensed for intravenous use for bowel cancer. Whereas ranibizumab is now licensed for nvAMD in the UK, no applications have been made to license bevacizumab for the treatment of nvAMD. Animal experiments and electrophysiological experimental in humans have not demonstrated toxicity in the retina (343). It does appear that bevacizumab can penetrate through all layers of the retina, which initial experiments had suggested would not be the case. Bevacizumab has been used off label in many patients worldwide and it has been suggested that the safety profile is similar to that for pegaptanib and ranibizumab (344).

In the CATT study (Comparison of AMD Treatment Trials) (345) 1185 participants were randomised to receive monthly 0.5mg ranibizumab; monthly 1.25mg bevacizumab; as needed ranibizumab or as needed bevacizumab, (as needed treatment consisting of one injection). At one year, those receiving monthly injections were randomised to either monthly or as needed groups. At two years, when relevant groups were combined, there was no significant difference in BCVA between ranibizumab and bevacizumab (mean change in BCVA -1.4 letters; 95% confidence intervals -3.7 to 0.8). Although the relative risk of a systemic adverse event was greater for bevacizumab than ranibizumab (RR 1.3, 95% CIs 1.07 to 1.57), the rate was greater in those receiving as needed bevacizumab than in the monthly group, and most of the events observed had not been seen when the drug was given systemically. Furthermore CATT was not powered for safety.

IVAN (alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation) (338) randomised 610 participants to receive either ranibizumab or bevacizumab either continuously (monthly) or discontinuously (three mandated injections if retreatment criteria were met). At one year comparison of BCVA between the ranibizumab and bevacizumab groups was inconclusive (mean difference -1.99 letters, 95% confidence intervals -4.04 to 0.06), while continuous and discontinuous regimens were equivalent (mean

difference -0.35, confidence intervals -2.40 to 1.70). Comparison of the two drugs and also of the two regimens showed equivalence for the secondary outcomes of near vision and contrast sensitivity. There was no difference between the drugs with regard to serious systemic adverse events, though the incidence of arteriothrombotic events or heart failure was less with bevacizumab than ranibizumab (odds ratio 0.23, 95% confidence intervals 0.05 to 1.07. Interestingly serum VEGF levels were lower with bevacizumab than ranibizumab ($P<0.0001$). Similarly IVAN was not powered for safety.

8.6.3. Aflibercept

Aflibercept (Eylea, Regeneron) is a fusion protein which inhibits all isoforms of VEGF-A as well as placental growth factor, thought to contribute to the pathogenic effects of CNV (346). Following demonstration of safety and tolerability in the CLEAR-IT 2 study (Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trials) (347), phase three trials were conducted. In VIEW1 (in the USA and Canada) and VIEW2 (in Europe, Asia-Pacific, Japan and Latin America), approximately 2500 participants with nvAMD were randomised to one of four regimens: i) monthly 0.5mg VEGF Trap-Eye; ii) monthly 2mg VEGF Trap-Eye; two-monthly 2mg VEGF Trap-Eye and iv) monthly 0.5mg ranibizumab (348). Each VEGF Trap-Eye arm was found to be non-inferior to monthly ranibizumab with regard to the proportion losing less than three lines of BCVA, average number of letters gained at one year and anatomic outcomes. No adverse safety signals emerged. The emergence of aflibercept has provoked much discussion about the relative merits of anti-VEGF agents (349). For example a varying 'sawtooth' pattern' of macular thickness in the two-monthly groups in the VIEW trials was observed: this may or may not be clinically relevant as there was no effect on visual function evident in the trials. In November 2011 the Food. and Drugs Administration in the USA approved two-monthly VEGF Trap-Eye for nvAMD. Aflibercept has undergone a technology appraisal by NICE and is now recommended as a treatment for nvAMD in the UK (TA294).

Practical Points

Ranibizumab and aflibercept can be used to treat all subfoveal CNV. NICE currently recommends treatment with ranibizumab and aflibercept but not pegaptanib. Section 9 of these guidelines gives the criteria for initiating, continuing or discontinuing treatment.
Bevacizumab has similar functional efficacy as ranibizumab but it is unlicensed for intraocular use, and its "off –label" status in this context should be clearly stated prior to its use in patients.

8.6 Combination Treatments

8.6.1 PDT and anti-VEGF

A major limitation of VEGF inhibition therapy is the need for repeated intravitreal injection with its attendant risks of endophthalmitis, retinal detachment and traumatic cataract. vPDT's role as an adjunctive agent is currently being explored.

Combination treatments of ranibizumab and PDT have been tried and appear to reduce the need for retreatment, but visual results have not been as good as ranibizumab alone. A study, PROTECT using the same formulation of ranibizumab as in the MARINA and ANCHOR trials combined with PDT did not raise any safety concerns. This nonrandomized open-label controlled trial of 32 patients found that same day application of PDT and intravitreal ranibizumab followed by three monthly injections improved visual acuity by a mean of 6.9 letters; 25% of patients improved by > 3 lines by month 4. Retreatments were rarely required during the 9 month follow-up (350). Two prospective randomised double masked clinical trials recently reported results. In the 'DENALI' non-inferiority trial (351) monthly ranibizumab was compared with as needed ranibizumab (after a loading phase) in combination with either standard fluence or reduced fluence vPDT. In the MONT BLANC trial (352) as needed ranibizumab was compared with as needed combination treatment, in each case

after a loading phase of ranibizumab. Neither trial provided evidence to support the routine use of vPDT in combination with ranibizumab for nvAMD.
An exception is in the treatment of polypoidal choroidopathy, for which vPDT has been shown, in the 'EVEREST' study, to produce superior visual outcomes, either alone or in combination with ranibizumab, than ranibizumab alone (280).

8.6.2 Triple therapy- PDT + anti-VEGF + steroid

Trials are underway looking at triple therapy to treat macular degeneration. The logic behind this is that PDT will eradicate the existing CNV, the steroid will limit the inflammatory response and reduce further upregulation of VEGF and the anti -VEGF will prevent any further angiogenesis. Retrospective studies suggest that combination therapy may reduce the number of retreatments of anti-VEGF agent required (353, 354). A prospective case series of 104 patients looking at PDT reduced fluence + bevacizumab 1.5mg +dexamethasone 800mcg reported significant and sustained visual acuity improvement after only 1 cycle of treatment (355). The RADICAL study investigated the combination of reduced fluence vPDT, ranibizumab and intravitreal dexamethasone was a single masked randomised study. The numbers enrolled were small compared to other trials, and the results are available at clinicaltrials.gov (NCT00492284). Larger randomised controlled trials of therapies are warranted.

8.6.3 Radiotherapy and anti-VEGF

Although radiation monotherapy does not offer significant functional benefits, its role as an adjunct has been explored recently. The development of epimacular brachytherapy appeared to offer promise as this method which uses a limited vitrectomy and application of a beta emitting source to the macular region can deliver a dose of 24 Gy within a few minutes to a focally delineated area without exposure to other ocular structures. A theoretical advantage of this approach is the likelihood of improved retinal oxygenation from the vitrectomy. However the need for vitrectomy and the risk of radiation induced retinal vessel damage are important concerns. Data from the MERITAGE trial in the USA suggested

significant benefit for those with chronic active nvAMD in terms of both improved vision and a reduced need for ongoing anti VEGF treatment (356). However the phase 3 CABERNET trial (for treatment naive patients) (357) failed to replicate these findings. Reasons advanced for the disappointing results are that the vitrectomy increased the rate of cataract formation and increased clearance of the anti-VEGF drugs from the vitreous. Furthermore variability in dose delivery to the region of interest may have occurred as surgical skill and probe placement are critical factors. The MERLOT trial conducted in the UK, on patients failing to respond to anti-VEGF therapy (NCT01006538), is ongoing.

However a new device; the iRAY which can deliver highly collimated doses of radiation without invasive procedures has recently been developed and tested. A trial using this device in non treatment naïve patients who were VEGF dependent found a reduced need for continued anti VEGF therapy in eyes treated with a 16 or 24 Gy single dose of radiation compared to sham treated eyes (see section 8.4) (323). This trial, the INTREPID study, used the bespoke iRAY delivery system which is ergonomically designed in a manner akin to a slit lamp. The design of this device permitted a high dose rate focal delivery of electrons to the posterior pole with minimal gratuitous radiation to radio-sensitive ocular structures such as the lens and optic nerve. The iRAY device was included under Domain 2 “enhancing quality of life” in the catalogue of potential innovations; NHS outcomes framework which was launched in March 2013, (http://innovault.innovation.nhs.uk/pg/cv_blog/content/view/61465/network). Thus the use of radiotherapy as an adjunctive treatment remains a viable tool as it has the potential to reduce the need for high frequency treatment rates with anti-VEGF agents in the medium to longer term.

Practical points

The role of combination treatments is not yet established but PDT and radiotherapy continue to be investigated.

8.7 Emerging therapies

Treatments for exudative AMD are developing rapidly (358). Other methods of inhibiting the VEGF pathway are being investigated than molecules that directly bind VEGF such as mRNA or tyrosine kinase receptor inhibitors. Complement and integrin inhibitors are also being investigated. Different modes of drug delivery are also being developed.

9. Treatment Delivery

As previously described, the neovascular lesion in nvAMD leaks fluid which leads to the separation of tissue compartments and loculation of fluid within the neurosensory retina. In addition, these fragile new vessels can rupture leading to accumulation of blood between tissue compartments and within the neurosensory retina. Fibrosis is inevitable, resulting in permanent disruption of tissue architecture. Enlargement of the scotoma with permanent severe vision loss is almost inevitable, if the disease is allowed its natural course. As such, treatment must be undertaken without delay and preferably within two weeks of initial development of symptoms or detection of a treatable lesion.

9.1 Initiating treatment

It is recommended that a definitive diagnosis of CNV is made prior to initiating treatment. The CNV lesion type, location in relation to the fovea and size of lesion should be established and recorded in the medical notes.

Baseline investigations should include best corrected visual acuity, FFA and OCT.

Concomitant ocular diseases, along with relevant past medical history need to be documented e.g. IHD, hypertension, diabetes mellitus, although their presence is not a contraindication to treatment. Similarly medication including anticoagulant therapy should be recorded.

FFA protocol is covered in chapter 5.3.2 and 5.3.3. Fluorescein angiography may not be possible in patients with poor venous access or considered an

unacceptable risk in patients with a past history of fluorescein anaphylaxis or sensitivity.
The reason for omitting FFA should be explicitly documented in the patient's records.
OCT protocol is covered in chapter 5.3.or ICG protocol is covered in chapter 5.3.4
ICG should be considered in patients suspected of retinal angiomatous proliferation, idiopathic polypoidal choroidal vascaulopathy,or occult peri-papillary choroidal neovascular membranes extending to the fovea, to confirm diagnosis. The diagnosis will influence treatment options and prognosis.

9.2 Choice of therapy

It is recommended that ophthalmologists with knowledge and experience in the care of patients with AMD should initiate treatment and decide upon the type of therapy. Where it is not possible for the service to be delivered exclusively by such a person, it may be necessary for the AMD service to be delivered by a multidisciplinary team, with members trained to acceptable levels of competence as determined by clinical governance, and working under the supervision of a an experienced medical retinal expert.
The aim of treatment is the improvement or stabilisation of visual symptoms. The guiding principle should be that the treatment recommended is in the patient's best interests. The treatment recommendations should be guided by patient characteristics, type of lesion and logistics.
Information included in this section can also be found at
http://www.rcophth.ac.uk/docs/scientific/Ranibizumab_-_June_2008.pdf

Extrafoveal Lesions

Patients with extrafoveal (posterior edge of lesion located 200µm from the geometric centre of the fovea) small well defined classic CNV may be treated with focal thermal laser photocoagulation as described in the MPS protocol or

anti-VEGF therapy if the laser treatment induced scotoma might interfere with normal visual function.

In patients with extrafoveal CNV untreatable by argon laser who are asymptomatic, and where there is no demonstrable progression or threat to vision, observation may be advised.

In patients with large extrafoveal classic or occult CNV with progression, it is justifiable to offer alternative treatments as laser photocoagulation is not recommended.

Juxtafoveal Lesions

As there is a risk that argon laser to a juxtafoveal CNV (lesions with the posterior edge lying between 1 and 199µm from the geometric centre of the fovea) will result in severe visual loss owing to proximity to the geometric centre of the fovea, laser photocoagulation is not recommended. The damage results from direct foveal photoreceptor and RPE destruction, or later encroachment of the scar on the fovea. The patient should be offered alternative retinal sparing therapies.

Subfoveal Lesions

Following the technology appraisals by NICE (NICE TA155) on ranibizumab re-issued in May 2012, and on aflibercept in July 2013 (NICE TA294), the licensed treatment options for lesions with subfoveal involvement are the anti-VEGF agents ranibizumab 0.5 mg or aflibercept 2mg. The College has produced a statement, in July 2013, on the final guidance from NICE on aflibercept and also produced a statement on the use of bevacizumab in medical ophthalmology, including in AMD, published in December 2011 (http://www.rcophth.ac.uk/news.asp?section=24&itemid=649). Pegaptanib is not recommended by NICE. However, funding for pegaptanib may be sought from Commissioners on an exceptional case basis, for example if there is a documented allergy to other anti-VEGF agents. In addition, where treatment with

pegaptanib has resulted in good outcomes previously, such treatment may be continued.

In the Technology Appraisal 294 on aflibercept for nvAMD, NICE recommended aflibercept be used according to the same criteria as described for ranibizumab in NICE Technology Appraisal 155, until both could be appraised simulataneously. These are:

- the best-corrected visual acuity is between 6/12 and 6/96
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes

Treatment should be initiated with a licensed anti-VEGF agent if any of the following conditions are met:

- there is active subfoveal neovascularisation of any lesion type.
- in patients with occult CNV with minimal symptoms or without documented evidence of disease progression a period of observation may be undertaken. However if there is progression, treatment should be given. Progression is defined by the presence of at least one of the following criteria:
  - · The appearance of sight threatening CNV which was not previously suspected or thought to be present.
  - · Evidence of new haemorrhage and/or subretinal fluid.
  - · A documented recent visual decline in the presence of CNV.
  - · An increase in CNV size between visits.

  - BCVA should be equal to or better than Snellen visual acuity > 6/96 (LogMar 1.2 or 24 ETDRS letters).

  - There should be no significant permanent structural damage to the fovea before treatment is commenced. Significant structural damage is defined

as longstanding fibrosis or atrophy in the fovea, or a significant chronic disciform scar which, in the opinion of the treating clinician, would prevent the patient from deriving any functional benefit (i.e. prevent further loss of vision) from treatment.

Other considerations when commencing treatment

a) Bilateral active CNV lesions

It is reasonable to treat both eyes of an individual with a licensed anti-VEGF simultaneously, in the presence of bilateral active subfoveal CNV where the clinical features of each eye falls within the guidelines above. For simultaneous bilateral intravitreal injections, separate sets of instruments should be used for each eye. Similarly, separate vials of anti-VEGF agents should be used for each eye. The patient should be made aware of the usual cumulative risks of sequential injections either to each eye on separate visits or to both eyes on the same visit.

b) Predominantly haemorrhagic lesions

Foveal haemorrhage or haemorrhage of greater than 50% of the total CNV lesion, are not considered reasons to withhold treatment with a licensed anti-VEGF agent.

c) Raised intraocular pressure

Elevated intraocular pressure (IOP), even of >30mm Hg, should not preclude treatment provided the IOP is treated simultaneously.

d) Intraocular surgery

It is advised that in the presence of exudative AMD and cataracts, the former should be treated and CNV activity controlled prior to cataract surgery, wherever possible. If CNV is diagnosed after intraocular surgery or there is reactivation of

an existing CNV, treatment with a licensed anti-VEGF agent can be commenced immediately, however attention should be paid to the cataract wound.

Criteria for not commencing treatment

It is recommended that treatment with a licensed anti-VEGF agent should not be commenced in the presence of:

a) permanent structural damage in the fovea where prevention of further visual loss is not possible.

b) evidence or suspicion of hypersensitivity to a licensed anti-VEGF agent. Such evidence should lead to avoidance of therapy, and alternate treatments sought.

9.3 Intravitreal drug delivery

The Summary of Product Characteristics for the licensed anti-VEGF agents state that they must only be administered by a qualified doctor experienced in administering intravitreal injections. In 2013 the Royal College of Ophthalmologists published a statement on intravitreal injections of anti-VEGF agents by non-medical health care professionals (HCPs). The College view was that where circumstances and facilities allow, the injection should be given by a specialist doctor trained in the procedure. However it is reasonable for non-medical HCPS to administer injections if certain stipulations are met, listed in the statement.

There are potentially serious adverse events associated with intravitreal injections: endophthalmitis, cataract, vitreous haemorrhage and retinal detachment. IVT Procedure Guidelines are available on the RCOphth website http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines_intravitreal_injections_guidelines2009.pdf

Location

The procedure may be carried out in theatre or a dedicated clean room in the outpatients' department. For outpatient delivery, the room must be an enclosed, dedicated clean room that is free from interruptions. The room must have good

illumination, washable floors (UK Health & Safety Regulations) and the ceiling should be non-particulate in nature (no dust or debris should be able to fall on to operative field). Facilities for surgeon's hand-washing, and the wearing of sterile gloves are essential. Resuscitation facilities must be readily available. A table, couch or reclining chair which allows the patient to lie supine is necessary. The room size should be such as to allow enough space on either side of the table to facilitate the movement of the surgeon and the surgical trolley.

Minimum Equipment requirement

Sterile eyelid speculum, sterile cotton buds, sterile ophthalmic drape, sterile calipers (millimetre gauge), povidone 5% solution (aqueous based)/iodine wash, syringe (drug may be pre-loaded), drawing up needle, 30 gauge injection needle (a wider needle bore to be used with triamcinolone to prevent crystals jamming during injection), topical anaesthetic. Surgical gloves are mandatory. A surgical mask can be worn if desired.

Anaesthetic

Topical anaesthesia will suffice in most cases especially when instilled copiously over 5-10minutes prior to injection. Supplementary sub-conjunctival or sub-tenon 1%- 2% lignocaine injection can be given if necessary.

Patient preparation

On the day of intra-vitreal injection, visual acuity and intra-ocular pressure check are not necessary if a two-stop approach to treatment is carried out. Application of a single use mydriatic to achieve pupillary dilatation is recommended. Check the patient can count fingers immediately after the injection to ensure the retinal artery is perfused.

Eye Preparation

Topical anaesthesia, followed by Povidone 5% aqueous solution (or equivalent) applied to eyelids, eyelid margins and into the conjunctival sac with a contact

time of 60 seconds, is a minimal requirement. Pre-injection broad spectrum topical antibiotics may be used in addition to the minimal requirements at the discretion of the treating clinician (359).

Technique:
Patient preparation
Eye preparation
Drape patient
Insert eyelid speculum, ensure it is well positioned with eyelid margins and eyelashes are away from the site of injection
Iodine solution
Instruct the patient to direct gaze away from the injection site
Mark the injection site using the calipers (avoid the horizontal meridians of the globe):

- aphakic/pseudo-phakic patients 3.0-3.5mm from limbus
- phakic patients 3.5-4.0mm from limbus

Use of forceps to steady the eye may occasionally be necessary
The needle of the syringe containing the intravitreal drug is inserted perpendicular through the sclera with tip aimed towards the centre of the globe (avoid any contact with the posterior lens)
Inject appropriate volume (0.05-0.1ml) of the therapeutic agent slowly and carefully
To avoid vitreous reflux the needle should be held in place for 5 seconds and then removed slowly.
A sterile cotton-tipped applicator placed at the site of penetration is also helpful in preventing reflux
Check the patient can count fingers or can see hand movements to ensure central retinal artery is perfused.

If patient cannot perceive light and eye is hard on digital palpation:

- Check central retinal artery appearance. It would be very unusual for a volume of 0.05ml of fluid to cause central retinal artery closure. If pressure remains high with vision of no light perception consider anterior chamber paracentesis. Such decompression needs to be achieved within 3-5 minutes. Care needs to be taken if the patient is phakic.
- If pressure remains high but vision is returning consider intravenous acetazolamide.

Post-injection management (following injection of licensed anti-VEGF or triamcinolone acetonide):
Immediate post-injection examination may be performed on a slit-lamp assessing the wound site for vitreous wick, measuring intra-ocular pressure, assessing central retinal artery and fundoscopy. However this is not mandatory.
Consideration should be given to checking the intraocular pressure following intravitreal injection of triamcinolone as it is known to be significantly associated with an intraocular pressure rise. However, this immediate post-operative IOP check is unnecessary with smaller volume injections of $\leq$ 0.09ml especially for agents not known to be associated with IOP rise.
Routine post-injection antibiotics are not recommended as there is no evidence that their use reduces the incidence of endophthalmitis (360), but can be used at the discretion of the treating clinician. Patients should be given clear instructions what to expect and a telephone number to contact for advice in the event of problem. Urgent attendance at hospital is required if endophthalmitis is suspected.
Clinic review 4-8 weeks post-injection should be arranged depending upon therapeutic agent.

9.4 Outcomes to be measured
It is good clinical practice to measure visual acuity at every visit, undertake a biomicroscopic examination of the retina and posterior pole structures and

perform an OCT scan of the macula of the eye being treated. The fellow eye should also be managed in the same manner if on active treatment for nvAMD. A fellow eye with early AMD should be examined regularly for incipient nvAMD. A fellow eye with an end stage disciform scar need not be observed. Near visual acuity and low vision support may also be necessary. Fluorescein and indocyanine green angiography are necessary for diagnosis and may be required to revise diagnosis and when considering a change in treatment

Below are the list of examinations:

1. Distance visual acuity
2. OCT
3. Fundus biomicroscopy
4. Fundus photography
4. FFA

Other outcomes of interest include contrast sensitivity which is impaired in age related macular degeneration.

The collection of quality of life data does not need to be undertaken routinely on patients receiving treatment for age related macular degeneration. Quality of life data collection will be necessary to estimate cost effectiveness of treatment. Quality of life data may need to be collected as part of commissioning arrangements for patients receiving treatment.

The assessment of visual fields, reading speed and electro-diagnostics (ERG) is recommended only as part of a clinical trial, or at the treating ophthalmologist's discretion.

9.5 Follow up intervals

Ranibizumab and aflibercept are initiated with a 'loading' phase of three injections given monthly for three consecutive doses, followed by a maintenance phase in which patients are monitored with BCVA, history, examination, OCT and/or angiographic examination. The interval between two doses should not be shorter than 4 weeks normally for ranibizumab or 8 weeks for aflibercept. However, there are instances where the occasional patient with hyperactive

lesions may for a short time require more intensive therapy.
It is expected that all patients will receive 3 loading doses of ranibizumab, or aflibercept unless there are particular contraindications. Pegaptanib (Macugen) is given by 6 weekly injections. However current recommendations from NICE are that it is not cost-effective as a first line therapy in the treatment of wet macular degeneration.

9.6 Re-treatment decision making
It is recommended that only ophthalmologists experienced in the management of patients with age related macular degeneration should decide on initiating treatment and permanent cessation of treatment.

Criteria for Continuation of treatment
After the three initial doses, ranibizumab should be continued at 4 weekly intervals, aflibercept at 8 weekly intervals and pegaptanib at 6 weekly intervals if:

a) There is persistent evidence of lesion activity
b) The lesion continues to respond to repeated treatment
c) There are no contra-indications (see below) to continuing treatment.

Disease activity is denoted by retinal, subretinal, or sub-RPE fluid or haemorrhage, as determined clinically and/or on OCT, lesion growth on FFA (morphological), and/or deterioration of vision (functional).
Where there is recurrence of CNV activity, treatment is reinstated until lesion stabilisation is achieved as indicated by BCVA and or lesion morphology.

9.7 Drug Holding and Cessation of therapy
Consider temporarily discontinuing treatment if:
(1) There is no disease activity
The disease should be considered to have become inactive when there is:

a) Absence of FFA leakage or other evidence of disease activity in the form of increasing lesion size, or new haemorrhage or exudates (i.e. no increase in lesion size, new haemorrhage or exudates) even if there is

persistent fluid (intraretinal cysts or tubulation denoting chronic changes) on OCT.

b) No re-appearance or further worsening of OCT indicators of CNV disease activity on subsequent follow up following recent discontinuation of treatment.

b) No additional lesion growth or other new signs of disease activity on subsequent follow up following recent discontinuation of treatment.

c) No deterioration in vision that can be attributed to CNV activity.

(2) There has been one or more adverse events related to drug or injection procedure including:

a) endophthalmitis

b) retinal detachment

c) severe uncontrolled uveitis

d) ongoing periocular infections

e) other serious ocular complications attributable to an anti-VEGF agent or injection procedure

f) thrombo-embolic phenomena, including MI or CVA in the preceding 3 months, or recurrent thrombo-embolic phenomena which are thought to be related to treatment with an anti-VEGF agent

g) other serious adverse events (SAE) e.g. hospitalisation

Consider discontinuing treatment permanently if there is:

1. A hypersensitivity reaction to a licensed anti-VEGF agent is established or suspected. A change to pegaptanib, if not previously used, or PDT is recommended.

2. Reduction of BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributable to AMD in the absence of other pathology.

3. Reduction in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline as this may indicate lack of responsiveness to treatment, or adverse event or both

4. There is evidence of deterioration of the lesion morphology despite optimum treatment. Such evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over a 3 consecutive visits.

9.8 Discharging patient from Hospital eye clinic follow up

Consider discharging the patient from long term hospital follow up if:

1. The decision to discontinue a licensed anti-VEGF agent permanently has been made
2. There is no evidence of other ocular pathology requiring investigation or treatment
3. There is low risk of further worsening or reactivation of nvAMD that could benefit from restarting treatment e.g. very poor central vision and a large, non-progressive, macular scar.

Practical Points

Patients should be advised of the need for frequent monitoring when commencing a course of intravitreal drug treatment for AMD. This will be every 4-8 weeks depending on the licensed anti-VEGF used. Treatment and follow-up may need to be continued for up to and beyond 2 years.

Further research is required into appropriate duration and optimal regimen in terms of frequency of injections. It still remains to be seen whether less frequent dosing of ranibizumab or aflibercept than that used in the pivotal trials will achieve the same visual benefit.

Licensed anti-VEGF treatment will only improve vision in a third of patients. The majority will maintain vision and some 10% will not respond to therapy.

Evidence suggests aflibercept treatment outcomes are similar to those of ranibizumab.

Pegaptanib treatment will reduce the risk of moderate and severe visual loss but most patients will still lose some vision over 2 years.

Patients should understand the risk associated with intravitreal injections and be instructed to report symptoms suggestive of endophthalmitis without delay.

10. Summary –Treatment Algorithm

Recommendations for Treatment of Neovascular AMD
Licensed intravitreal anti-VEGF may be used to treat all lesion types: classic, predominantly classic, minimally classic, occult and RAP lesions. PDT monotherapy or in combination with licensed anti-VEGF therapy is recommended in eyes with IPCV.

Extrafoveal CNV: Patients with extrafoveal CNV should be treated with focal laser photocoagulation as described in the MPS protocol or licensed anti-VEGF therapy if the laser treatment induced scotoma might interfere with normal visual function.
However, in patients with large extrafoveal classic CNV, or occult CNV with progression, it is justifiable to offer alternative treatment similar to that of juxtafoveal lesions. Where no progression is demonstrable, or vision is not threatened observation is advised.

Laser photocoagulation is not recommended for patients with subfoveal or juxtafoveal CNV because of the immediate visual loss that results from foveal photoreceptor and RPE damage, or later encroachment of the scar on the fovea.

Subfoveal/juxtafoveal CNV: it is expected that eyes with subfoveal/juxtafoveal CNV of all lesion types will benefit from treatment.

Predominantly classic subfoveal/juxtafoveal CNV: licensed anti-VEGF treatment is recommended first line. However patients with predominantly classic AMD with subfoveal and juxtafoveal location could be offered PDT or combination treatment in the first instance if regular attendance at clinic is difficult. Visual outcomes with combination therapy may not be as good as with monotherapy with licensed anti-VEGF.

Occult subfoveal/juxtafoveal CNV: the use of licensed anti-VEGF is recommended if there is evidence of recent disease progression.

Minimally classic subfoveal/juxtafoveal CNV: Intraocular injections of licensed anti-VEGF should be considered as first line treatment.

Treatment of RAP and IPCV lesions are based on clinical case series and expert opinion as these lesions have not been systematically studied in large randomised clinical trials.

Retinal angiomatous proliferations (RAPs): do not respond well to PDT alone. There are reports of successful treatment of eyes with RAPs treated with repeated injections of licensed anti-VEGFs.

Idiopathic Polypoidal Choroidal Vasculopathy (IPCV): normally only patients with macular involvement are treated, unless the central vision is threatened by persistent or progressive exudation, or large subretinal/retinal haemorrhage. Direct laser photocoagulation can be used for extrafoveal IPCV. Active and symptomatic IPCV with subfoveal/juxtafoveal lesions can be treated with PDT monotherapy or in combination with licensed anti-VEGF therapy. The EVEREST

Study has shown that PDT given either alone or in combination with ranibizumab provides the best outcome in the treatment of IPCV, as anti-VEGF monotherapy results are suboptimal.

When recommending intraocular bevacizumab (Avastin) it is extremely important to inform patients that it is unlicensed for this indication and that it has not undergone the usual rigorous clinical trials and independent evaluation by regulatory authorities. Adequate follow-up information must also be maintained on these patients, and recorded appropriately.

Practical Points.
All lesion types of neovascular AMD benefit from treatment with licensed anti-VEGF therapy.

IPCV lesions respond best to PDT monotherapy or in combination with intravitreal injections of anti-VEGF.

11. Management of non- neovascular AMD

11.1 Monitoring Progression

The term “dry AMD” is commonly used to cover a range of fundus signs (1), including drusen and pigmentary changes to patchy areas of atrophy to geographic atrophy (GA). This can be very confusing for patients. Terms need to be used carefully. Early AMD should be used to describe drusen and pigmentary changes and not the term ‘dry’ AMD. To avoid confusion the term dry AMD should be reserved for geographic atrophy.

Fundus photography has limited value in assessing and monitoring the progression of atrophic areas. Although it has not been proven scientifically, autofluorescence (AF) imaging is now believed to be the method of choice in

imaging GA and hence monitoring of progression of non-neovascular AMD [359]
Adaptive optics to monitor individual photoreceptors has also been utilised as an endpoint in clinical trials for dry AMD but is not widely available in clinical practice.

11.2 Strategies for prevention of late AMD

11.2.1 Laser

The observation of disappearance of drusen after focal laser treatment has led to numerous clinical trials of using laser as prophylactic treatment of patients with large drusen (360-363). A Cochrane review examining studies using laser of drusen to prevent nvAMD found that while laser does promote disappearance of drusen, there is no evidence that this prevents subsequent CNV or visual loss (361). Instead of using focal laser, a large spot size lower power (diffuse) laser is currently under investigation.

11.2.2 Vitamins/Zinc/Antioxidants/Lutein/ Docoshexaenoic acid

See section 6.2.3

11.3 Progressive geographic atrophy

11.3.1 Prediction of progression from early AMD to GA

By examining the serial fundus photographs in the AREDS with GA at the last follow up, the progression was usually characterized by large drusen formation and development of hyperpigmentation, followed by regression of drusen, appearance of hypopigmentation, and ultimately development of GA, sometimes preceded by the appearance of refractile deposits (362).
AF imaging of patients with GA can be sub-classified based on the appearance of the junctional zone and generalised background. Areas of increased autofluorescence surrounding GA are likely to progress to atrophic area in the short term (363).

11.3.2 Cellular protection

Geographic atrophy is in effect a cellular death of RPE cells. By preventing the cells from going into apoptosis, it might be possible to slow the progression of GA. Several studies are underway to explore this option.

11.4 Management

11.4.1 Low vision rehabilitation

In many patients with advanced non-neovascular AMD, reading is difficult despite relatively good distance visual acuity. Magnifiers and low vision aids are required for these patients. Using computers in tablet form with inbuilt ability to enhance contrast, change background and zoom for magnification rapidly can be helpful. For those who have lost the foveal vision, a preferential retinal locus (PRL) will develop over time. There is some evidence that training using biofeedback can help to develop a more stable PRL.

11.4.2 Surgical options

Several devices exist designed as intraocular optical aids for end-stage AMD, reviewed by Singer et al (364). Two devices have CE marks: the Implantable Miniature Telescope (IMT) prosthesis (Vision-Care Ophthalmic Technologies, Saratoga, California, USA) (also approved by the FDA) and the IOL-VIP system (IOL-VIP System, Soleko, Pontecorvo, Italy).

The IMT is designed to overcome bilateral central scotomata resulting from end-stage AMD; that is from a fovea-involving disciform scar or atrophic region. It is intended to enlarge the retinal image of the central field (364), magnifiying objects whose image would otherwise fall sufficiently within the scotoma to prevent recognition. The magnification allows the object to be resolved at an eccentric fixation point. The logic is that an IMT in one eye provides usable central vision, while the other eye, without an IMT, provides peripheral vision. IMT002 was a multicentre prospective open-label study investigating the safety and efficacy of the IMT in participants over the age of 55 years, with BCVA between 20/80 and 20/800 due to stable and untreatable GA or disciform scars

(365). Two-hundred and six patients received the IMT in their worse eye. The fellow eyes acted as controls.

Evaluation of safety of the device was the first stated aim of the study. One eye (0.6%) in the IMT group lost three or more lines of BCVA, compared to 13 (7.5%) control eyes (p=0.0013). After two years follow-up there were no cases of retinal detachment or visually significant posterior capsular thickening. At two years, 8 patients (3.9% of the 206 who received implants) had the implants removed; two due to prosthesis failure and four on patient request (three requested removal because of excessive glare in bright light and one because of reduced depth perception and reduced peripheral vision). The most clinically significant safety concern related to corneal health. Two of the 8 who underwent IMT removal had corneal oedema requiring corneal graft surgery. Mean endothelial cell loss at three months was 20% in IMT eyes, but endothelial cell density stabilised thereafter to the two year study end-point. Evaluation of efficacy was the second aim of the study. For the 174 patients for who data was available at two years, a statistically significantly greater (p=0.0001) proportion of eyes implanted with the telescope had a BCVA improvement compared to control eyes. Furthermore the gains were clinically meaningful, at a mean of 3.2 lines for IMT eyes, compared to 0.5 lines for control eyes. On average BCVA gains were greater with the telescope providing 3x magnification compared to 2.2x magnification; there was no evidence that the reduced width of field provided by the IMT offering greater magnification was a problem to patients in the study. Furthermore visual gains were still significantly greater for eyes receiving the IMT compared to control eyes if the control eye underwent cataract extraction and IOL implantation during the study period. These potential gains are reflected by an improvement in quality of life recorded at one year in study participants, and it is said to be cost-effective by conventional standards (366).

The IOL-VIP system consists of a high minus IOL in the capsular bag and a high plus IOL in the anterior chamber. The preferred retinal locus is identified pre-operatively, to determine the optimum point of eccentric fixation which guides the surgeon as to the rotation position at which the IOL-VIP should be inserted, given

its built-in prismatic effect. Theoretical advantages are that it is possible to implant the IOL-VIP bilaterally as field of vision is not so restricted by the lens system to prohibit navigation, thus preserving depth of vision. Evidence for its safety and efficacy is provided by a pilot study. In a case series of 40 eyes of 35 consecutive patients (367) all patients experienced an improvement in BCVA and reading distance, and no serious adverse events occurred.

Implant technology is in evolution with new anterior and posterior segment implants under development, and further research is needed on their safety and efficacy. The highest quality evidence on these devices, a non-randomised open label prospective study, supports the use of the IMT for end-stage AMD. However there are several important caveats on their use, beginning with appropriate patient selection. In particular corneal endothelial health should be assessed, although in the IMT002 trial most endothelial cell loss was temporally related to the surgery.

Summary.

Such devices may be a suitable option for some patients, bearing in mind the following pre-operative caveats.Use of intraocular optical aids should follow a carefully pre-planned scheme:

Pre-operatively:

- careful examination for the presence or absence of guttatae or posterior corneal dystrophy
- measurement of endothelial cell density and corneal thickness
- evaluation of eye dominance (368)
- counselling to manage patients' expectations about likely improvements, possible adverse effects, the fact that long-term efficacy and safety outcomes are unknown (particularly as their AMD may advance), and the need for visual rehabilitation.

Surgically:

- A specific surgical technique is advised (365)

Post-operatively:

- visual rehabilitation services should be available to help the patient adjust to, for example, the lack of depth perception, and the skill of being able to find an object of interest with the other eye, and then study the object with the IMT eye. Pre-operative sessions using an external telescope may help to these ends.
- NICE guidance (IPG272) on implantation of miniature lens systems for advanced AMD, issued in August 2008, advices that the procedure only be used with "special arrangements for clinical governance, consent and audit or research".

Practical Points

Treatment for non-neovascular AMD is limited and consists mainly of counselling, smoking cessation, visual rehabilitation and prescription of AREDS style vitamins to reduce risk of progression in those expected to benefit. Clinical trials of novel therapies are now taking place but are not currently available in clinical practice.

12. Management of Chronic/Long standing vision loss

12.1 The diagnosis session in clinic – general remarks

a. Breaking bad news. Patients report that after receiving news that their eye condition is not treatable, they tend not to hear further information during the consultation. It is therefore important that patients are given written information at the end of the consultation concerning their eye condition, available rehabilitation services and useful contact numbers.

b. Avoid ‘diagnose and immediate discharge’. Patients with macular disease who have lesions which are not treatable with current therapies are often seen only once in the eye clinic and then discharged. They can be unaware of what to expect in the future or where they can obtain relevant information or how to find their way through the maze of services and

organisations. Although there may seem little advantage in seeing the patient a second time, because most are not able to take in information after receiving bad news, a follow up visit is of benefit to receive further information and ask questions. They must be given contact details of someone they can come back and talk to. This may be an Eye Clinic Liaison Officer (ECLO) who may be available at the time of diagnosis also.

c. The clinic experience at time of diagnosis has an impact on the way patients deal with their diagnosis and visual impairment. Patients frequently report that the diagnosis was given in an uncaring manner. A good initial experience at the hospital will almost certainly help the patient's future outlook, expectations and achievements. A satisfactory patient experience can only be achieved by good training.

d. Importance of signposting.
Receiving a diagnosis without the follow up information leaves patients feeling lost and isolated. They should be given appropriate information about support services such as visual rehabilitation officers and low vision services. Charities such as local societies, the RNIB, and the Macular Society offer wide range of services such as telephone advice and counselling services and local support groups.

e. Provide literature in the clinic. Patients appreciate being given information regarding their condition that can be read at leisure. It should be the responsibility of staff in the clinic to make information leaflets available and ensure that patients are offered them before leaving. The Macular Society and others have a wide range of materials in large print and audio.

f. Staff Training. Empathetic handling of a new diagnosis for a patient is a responsibility for the whole unit; continuous staff training is needed. All staff in a unit should be aware of the impact of diagnosis on patients.

g. Senior oversight. There should be senior ophthalmological oversight embedded in quality systems.

12.2 What the patient needs to know:

a. Clear diagnosis. Make sure the individual knows the name of the condition causing their sight loss and whether they have early AMD or late AMD of the exudative (wet) or atrophic (dry) type AMD or a combination of these. The information should be given in writing (large print) as well as verbally. This means that when they are ready to seek further advice and information they have accurate information about their condition. A vague description such as 'you have an eye condition to do with ageing' is not acceptable. An explanation of AMD must given as set out as above.

b. Vision prognosis – Provide clear information about the outlook for their vision: Will it develop in the second eye? If it is 'dry' could it become 'wet'? It is very important that education regarding the second eye is given. Patients must know how to obtain a new appointment urgently if they develop distortion or blurring in their second eye.

Some professional advocate the use of Amsler grids for self-monitoring, while others advise patients to use any straight line in their environment. Either is acceptable as long as the patient understands the nature and need for regular self-monitoring for new symptoms, such as distortion, in their second eye.

c. Treatment options if they exist.

- All eye department staff need to be aware that even if treatment is not appropriate for a patient with sight loss, individuals can be helped by a range of non-medical supportive measures.
- Eye Departments wherever they are located need to be aware of what is currently available to treat AMD, in the context of the NHS and current NICE guidelines, and if not able to offer one of the current treatments they must make patients aware of the full range of treatments available both on the NHS and privately.
- Phrases such as "nothing more can be done" in a medical sense should be avoided as this terminology can be devastating and unhelpful. The lack of a current therapy does not mean that help in other forms is not available.

- Interventions which can help the individual come to terms with their sight loss, retain their independence, and improve their function and quality life include information about the condition and prognosis, emotional support, counselling, a low vision assessment and practical input such as rehabilitation covering daily living skills, mobility and the benefits of lighting, colour and contrast in maximising the use of residual sight. Some awareness of the research in the area of retinal repair is helpful as many patients will wish to discuss the current research strategies; two examples are stem cells and electronic eye research.
- All staff and the patient need to be aware of the need to treat exudative AMD urgently. Patients should be told to contact the clinic if they have not received an appointment for treatment or further assessment within 2 weeks, also if there follow up appointment has been extended beyond 4-6 weeks.

d. Hallucinations -Charles Bonnet Syndrome (CBS).

Many patients with macular degeneration suffer or will experience visual hallucinations. People see different images, from simple patterns of straight lines to detailed pictures of people or buildings. These can be disturbing, and may not be voluntarily mentioned by patients to friends, family or the medical profession as sufferers may be concerned that they might be developing a serious mental illness. The anxiety is more damaging than the hallucinations themselves. Patients should be alerted to the possibility of CBS which typically improves by 18 months but can last many years. The Macular Society is familiar with the condition and can talk to patients and provide a leaflet. It is recommended that clinicians educate all relevant clinic staff about CBS, including receptionists and technicians.

e. Risk and improvement factors (see also section 6). Patients have no control over their age, genes or gender but they should be alerted to the other risk factors itemized below.

Smoking is a recognised risk factor for both dry and wet AMD. All patients with macular degeneration/ dystrophy should be advised to stop smoking. The NHS Stop Smoking Service telephone number is 0800 022 4332, or advice can be found on: http://smokefree.nhs.uk/, and help can be sought from their general practitioner. Recent studies show that smoking reduces the protective effects of antioxidants in the eye and damages the structure of the eye. [Detailed references for these studies can be found elsewhere in RCO guidelines and patient information sheets concerning smoking]. Smokers are three times more likely to develop AMD than non-smokers.

A diet rich in fruit and vegetables (sources of antioxidant vitamins), oily fish (source of omega-3 fatty acids) and sources of lutein/zeaxanthin (fruit and vegetables and eggs) is recommended. These measures are not proven conclusively to be beneficial and would not be expected to be harmful, and may be useful given what we know about the biology of the retina. With regard to nutritional supplements there are now many a vast number of different nutritional supplements for eye health available. Only the AREDS formula is proven to be beneficial in people with intermediate and advanced AMD but note: beta-carotene is contraindicated in smokers and potential side-effects of high dose zinc (eg hospitalisation for genitourinary conditions in men) (see also sections 6.1.4 and 6.2.3).Other supplements are currently under evaluation. The Carotenoids with Coantioxidants in Age-Related Maculopathy trial (CARMA) was a randomised double-masked placebo controlled clinical trial of oral supplements containing lutein, zeaxanthin, vitamin C, vitamin E, copper, and zinc, in 433 participants with early AMD in one eye or AMD in one eye with late AMD in the other (369). At three years functional and morphological improvements were evident, with the group given supplements having BCVA 4.8 letters better than the placebo group on average. In AREDS2 (68) no extra reduction in risk of progression to advanced AMD was evident by the addition of lutein and zeaxanthin, or omega-3 long chain polyunsaturated fatty acids, or all of these to the AREDS formulation.

Bright sunlight may be a contributory factor in the development of AMD but this is not proven. It is certainly true that patients with AMD are severely affected by the glare of sunlight and therefore good quality anti-glare lenses are essential. The Macular Society leaflet ‘Anti-glare Spectacles’ provides further information.

f. Continuing ocular exams – why and how often

The importance of ongoing regular eye examinations must be clearly explained to the patient, especially if they are likely to be discharged from the hospital system. Too often individuals never attend for any form of eye examination once diagnosis of a condition leading to sight loss has occurred, failing to understand that an eye examination is a good indicator of general health and provides an early warning for the development of other eye conditions. Cataract may worsen over the years reducing vision further and removal may be indicated.

Individuals should be advised to attend their optician at least every two years or more frequently if relevant. It may be necessary to explain the GOS system and their possible entitlement to a “free” eye examination.

There are restrictions on how often a person can have a free eye examination, in which case they will be charged the private eye examination fee.

They are entitled to NHS free eye examination in several circumstances, including being aged 60 years or more in any region of the UK.

Updates on categories entitled to free eye tests can be found online

g. Date of next appointment – If under treatment will require regular review. If discharged needs information for rapid review if condition recurs.

h. Change of vision. Individuals must be advised what they should do if they experiences a sudden change in vision, this may be to contact or attend the eye department within 1 week preferably. The eye department staff must be aware of the need for this group of patients to be seen urgently and have information and mechanisms in place to allow ease and rapidity of access.

12.3 Referral to rehabilitation and low vision services

a. If an individual has sight loss then it is vital that they be offered the opportunity of accessing low vision support and advice at an early stage.

Advice and use of task lighting and magnifiers reduce the early impact of sight loss and the risk of falls. Do not wait until all treatment options have been explored or until an individual's vision deteriorates to a level that registration as blind/ severely sight impaired or as partially sighted/ sight impaired becomes appropriate; before considering referring an individual to low vision and rehabilitation services.

b. Early advice and support means that an individual can learn how to use their remaining vision more effectively, retaining independence and confidence. It is also far easier to learn the principles of using optical low vision aids with the lower powers and the skills can be transferred to the higher powers later if needed. The longer it is left the more difficult it is to help a person overcome any loss of confidence in their abilities and the more likely that depression will occur.

General information from the NHS on living with low vision can be found at: http://www.nhs.uk/Livewell/Eyehealth/Pages/Livingwithlowvision.aspx

c. Find out where and what low vision services are available locally and refer your patients with low vision as soon as possible. Some may well be hospital based and others may be community based.

d. It should no longer be the case that access to a low vision service is certification/ registration led.

e. The NHS Eyecare Services Programme sets out what should be expected from a Low Vision Services, and is available online.

The principles:

- Access to rehab and low vision support will vary according to local arrangements. Clinicians should be present or represented on their local low vision committee. All local systems should adhere to these principles:
- Low vision services must reflect a multi-disciplinary, multi-agency approach that co-ordinates with other health and social care providers in the area, including services provided at the client's

residence at the time. This methodology ensures efficient and professional delivery of services.

- The services delivered must be based upon needs identified by clients and be sufficiently flexible to meet the disparate needs of its client group. There should be evidence of user participation in agreements on the setting up and implementation of pathways and protocols.
- Registration as sight impaired or severely sight impaired should not be a pre-requisite to accessing low vision services.
- Locally designed guidelines, pathways and protocols should be underpinned, whenever possible, by evidence based knowledge and accepted guidance. This must conform with and contribute to local clinical governance arrangements.
- Assessment. There should be a tailored needs-based assessment for each client following referral to the low vision service. A low vision assessment should always offer:
    - An eye health examination or evidence of recent examination or referral for examination according to local protocols.
    - A functional visual assessment
- After assessment the following should be offered, as appropriate, to the user:
    - Prescription/provision of appropriate optical/non-optical aids. The sale of some low vision aids is restricted to certain professionals or requires appropriate supervision. The supply/loan of aids should be governed by local protocol.
    - Advice on lighting, contrast and size, filters, tactile aids, electronic aids and other non-optical aids.
    - Training and/or therapy to enable optical and non-optical aids and other techniques to be used effectively.

- Links to broader rehabilitation services, such as home assessment and mobility as well as possible referral to structured therapy programmes and counselling.
- A review of benefits, welfare rights, concessions, support groups, (both local and national)
- Advice on access to the full range of low vision equipment available for purchase through local society resource centres or the RNIB or direct from retailers.

If an individual is experiencing difficulties because of problems with their sight they are entitled to an assessment of need by social services – they do not need to be registered as severely sight impaired or sight impaired. The level of support offered once an assessment of need has taken place will depend on locally decided criteria, but social services will be able to provide the client information as to the advice and support that is available in an area for people with sight loss and on any services for which they may be eligible.

In some areas social services will contact patients via the sensory impairment team rehabilitation officers for the visually impaired. Rehabilitation officers can provide training and support to a person with sight loss in their homes and local environment to cover daily living and mobility skills. The aim is to help an individual to retain their independence. They can also provide practical advice on how to use remaining vision effectively including the use of lighting, colour and contrast, which can be extremely beneficial even when there is minimal reduction to visual quality. It does not take long for people to lose confidence in their abilities as their sight deteriorates and for many this can lead to depression.

12.4 Registration

a. What is registration?

Practices may vary in different devolved administrations in the UK: region-specific information will be available from the local macular unit.

In England each local council keeps a register of sight impaired and severely sight impaired people living in its area. The register is held by the social services

or social work department, or by a local voluntary agency. The Certificate of Visual Impairment (CVI) was introduced in 2003 and is used to certify people as sight impaired or severely sight impaired. Concessions are calculated from the date of examination.

Hospital eye services can download the Word version of the CVI form for tailoring with their own contact details from the NHSweb, or by emailing OPDEnquiries@dh.gsi.gov.uk. This form formally certifies someone as sight impaired or severely sight impaired so that the local council can register him or her. Its second purpose is to record a standard range of diagnostic and other data that may be used for epidemiological analysis.

b. Why register somebody as severely sight impaired or sight impaired?

- Recent figures for the numbers of people registered as severely sight impaired or sight impaired have dropped significantly since the introduction of the (CVI). There may be many reasons for this, but it certainly does not reflect a drop in the numbers of people experiencing sight loss.
- If anything evidence based on the aging population predicts a sharp increase in the numbers of visually impaired individuals in the coming years. The services for people with sight loss are decreasing in some areas because of this drop in the numbers of people being registered.
- Epidemiology and prevalence data in the UK is based on the information contained within processed CVIs. If they are not completed for whatever reason then the future planning of health and social care services will be flawed.
- Social Services still base their budget allocations for support to people with sight loss on the number of CVIs that they receive. A reduction in registrations means that funding is allocated elsewhere. Many visually impaired people may not choose to be or are never offered the opportunity to become registered
- Certification is also the trigger for a review of benefits that an individual may receive, though these may vary in different devolved administrations in the UK. Examples of benefits that an individual may be entitled to include:

- Working tax credit
- There are increased personal income tax allowances for people who are registered blind, if they don't work allowances can be transferred to a working partner
- Parking concessions (e.g. A blue badge and discs permitting parking in restricted areas)
- Anyone who is registered blind can claim a 50% reduction in the cost of their television licence. (People over 75 do not have to pay for their TV licence).
- A free radio from the wireless for the blind fund
- Free directory enquiries service from BT
- Talking books from your local library service
- Concessionary travel
- Leisure centre concessions
- Free NHS sight test
- Free postage on items marked 'articles for the blind'

12.5 Signposts to others who will provide support

a. "Signposting" to others who can provide information, support and advice is vital. Not knowing how to access information or what help is available is cited by people with sight loss as the biggest barrier to coming to terms with their sight loss.

b. Signposting may be the provision of contact details so the individual can find out further information for themselves. Useful details to pass on would include:

- contact number for local sensory impairment teams – most councils have a single entry point duty telephone number
- Local VI society contact details
- Knowledge of local low vision services referral mechanisms and access criteria
- The Macular Society:

– the specialist national charity providing support for people with macular degeneration offers

- Information and support to individuals with sight loss through telephone helpline 0300 3030 111
- A range of leaflets in print or audio format
- Free telephone counselling
- Member quarterly magazine and annual journal summarising research developments
- Network of 250 volunteer led self support groups
- Website: www.macularsociety.org

13. AMD Referral Pathways

Referral systems can only work if discussions and training have been held locally between consultant ophthalmologists at specialist retinal centres, in District General Hospital eye units and with optometrists. The LOC should be involved with development of effective local pathways.

Consultant ophthalmologists should also be involved with their local low vision committee in order to establish effective pathways for referring patients into low vision and social services rehabilitation.

The Patient:

Self referral to:

- GP
- optician/optometrist
- hospital eye service

The aim at this stage must be to obtain a diagnosis

· GP	· The GP must regard self referrals with sudden onset central distortion in an older adult as potential exudative AMD and therefore as urgent · The GP can refer patients to an optometrist or to a District General Hospital Eye Service or to a Specialist medical retinal centre
· Optician/ · Optometrist	· Optometrists can refer exudative AMD cases directly to a specialist medical retinal centre with an established rapid access pathway · If this referral line has not been established patients may be sent to a District General Hospital Eye Service · The practice of sending the patient to the GP for onward referral is not necessary. It causes delay and is an unnecessary link in the chain. GPs should however be informed of the optician referral. · Referral forms to be used by optometrists for suspected exudative AMD patients can be found on this link: www.rcophth.ac.uk/core/core_picker/download.asp?id=533

· Eye Casualty	· Because of potential delays the Macular Society and RNIB help lines advise patients who have experienced a sudden change of vision to present themselves to eye casualty or obtain an urgent appointment in a specialist eye clinic. This will also apply to patients whose referral is delayed.

Diagnosis and Onward Referral

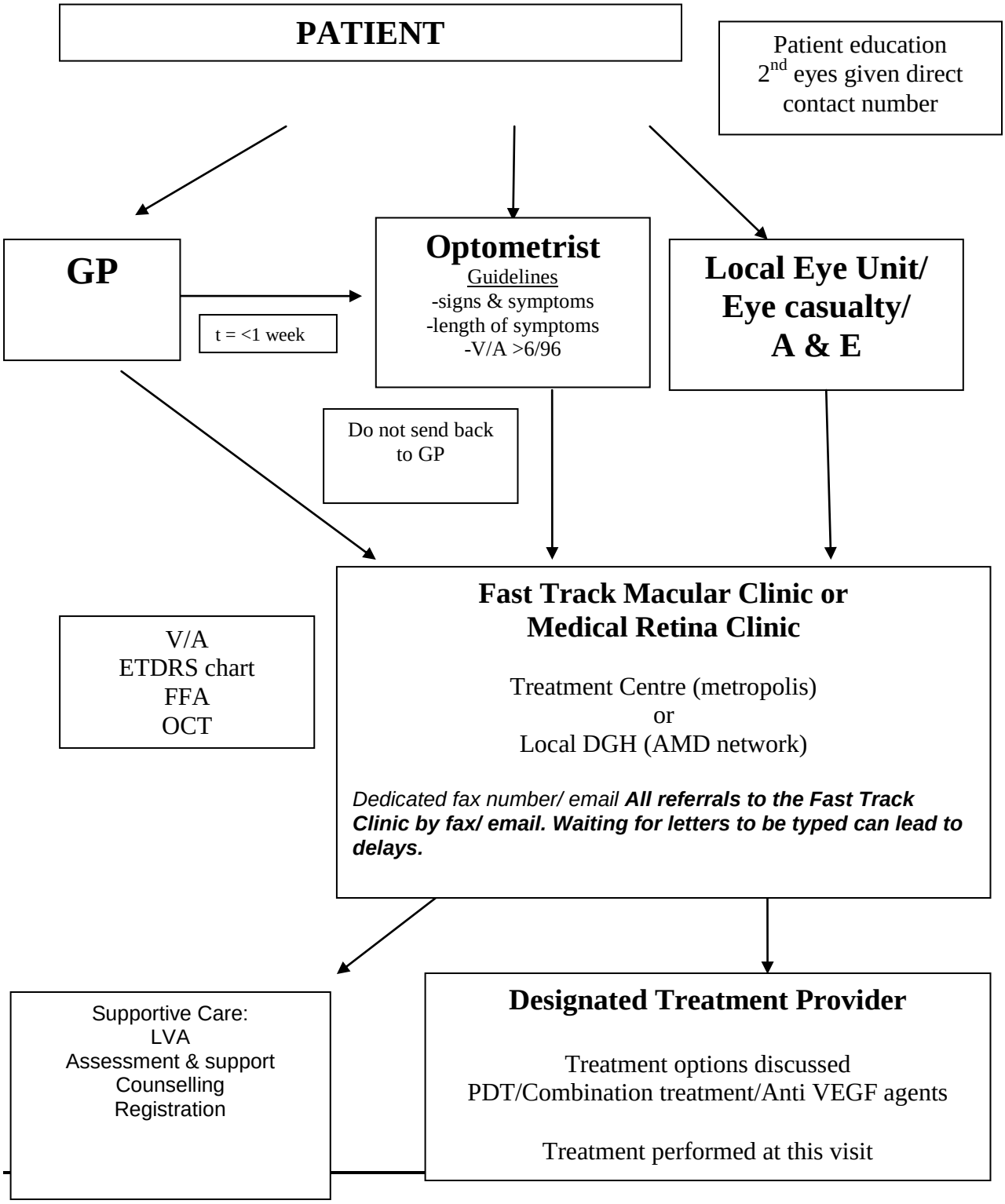
Exudative AMD	Geographic AMD
See next page for RCOphth referral chart and notes	
Give patient clear diagnosis and information	

- Best supportive care – see Section 12
- Referral to Low Vision Clinic for assessment and issue of low vision aids and for access to purchased low vision equipment
- Low vision clinic should notify social services where rehabilitation and a home visit is needed
- Registration using the CVI – this is likely to be in the patients interest if their sight is poor enough to meet the criteria
- Fitness to drive: clinician's assessment
- Sign posting to other agencies for information and support including counselling if needed:

For example:

- The Macular Society tel.: 0300 3030 111
- RNIB tel.: 0303 123 9999
- Local society for the visually impaired
- Nearest low vision / resource centre

WET AMD REFERRAL AND TREATMENT PATHWAY



Ideals to aim for:

t = <1 week from optometrist to Fast Track Clinic

t = <1 week from Fast Track Clinic to treatment

13.1 AMD Referral Pathways – notes to amplify the flow chart

As set out above, immediate rapid access to retinal specialists with expertise in the management of exudative AMD for all patients should be available, irrespective of geographic location. Patients should be seen by a specialist with medical retinal expertise within one week of diagnosis, and, there should be no more than one week between evaluation and treatment.

All patients suspected to have exudative AMD by the optometrist, general practitioner, or other health workers should be referred directly to the nearest AMD Centre, Eye Casualty, or Eye Clinic. Optometrists may be used for 'screening' or first examination of patients suspected of having exudative AMD. Referrals from the optometrist should be sent directly to an ophthalmology department, and should not pass through the general practitioner as such a route introduces unnecessary delays. Self referral or presentation to the Eye Casualty/Clinic or AMD Centre of exudative AMD should be encouraged, especially in patients who have second eye involvement. Optometrists with specialist interest ('Super Optometrist') are not recommended as such pathways will introduce unnecessary delays, and misdiagnoses.

Patient movement through the clinic

It is assumed that all new patients with CNV secondary to AMD referred to an AMD Centre, will undergo an extended assessment of vision, retinal imaging (FFA and OCT), ophthalmological examination, and then proceed to treatment within one week of diagnosis. At subsequent follow-up visits also, treatment would be expected to follow vision assessment, retinal imaging and ophthalmological assessment if indicated.

An integrated clinic for AMD patients is ideal. The pathway in such an integrated clinic would include visual assessments, OCT imaging. This may be in the form

of virtual clinics where colour and OCT imaging can be reviewed and patients requiring treatment can be identified. Medical assessments and FFA can be triggered from these clinics as appropriate. Treatments such as - intravitreal injections (and/or PDT 3 monthly) can be booked as appropriate subsequent to imaging review.

Movement of patients through the AMD clinic depends on whether a ‘ONE STOP’ or ‘TWO STOP’ model is adopted. In a ‘One Stop’ Model all examinations, investigations and treatments are undertaken on the same day, whilst in a ‘Two Stop’ Model examinations and investigations take place on one day, followed by treatments during a separate visit. A ‘one stop’ model is preferable as it minimises patient visits to the clinic, especially as some of them may have to travel significant distances. This has to be balanced against the moderate increase in the total time spent by each patient at each visit. Ultimately the model adopted by units will depend on staffing and resources.

Practical Points

Patients with exudative macular degeneration need to be assessed and treated promptly to gain maximum benefit from treatment. The Macular Specialist has a leading role in ensuring clear referral pathways exist both within Ophthalmology departments, and in liaising externally with community optometrists and other referrers to encourage appropriate rapid access pathways for referral and management of these patients.

Patients should have information provided in clinics with respect to support and rehabilitation services.

Extract from Macular Society articles.
By Dennis Lewis, of VINCE (Visual Impairment Network for Counselling and Emotional Support)

Two key facts

- 70% of newly-diagnosed blind and partially sighted people wanted someone to talk to about their fears and concerns but only 19% were offered this opportunity by their eye clinic (Patients Talking 2, 2001).
- Nearly 1 in 5 (17%) of blind and partially sighted people surveyed received no help or information in the eye clinic other than medical diagnosis and treatment. This rises to 1 in 3 (32%) for working age adults (Network 1000 Wave 2, 2008).

Evidence of depression in AMD

- Visual impairment is associated with a higher than normal risk of depression (370-372)(373). Of visually impaired older people, 13.5% were depressed compared with 4.6% of people with good vision (372).
- A survey of individuals registered blind and partially sighted in the past eight years reveals that only 8% of them were offered counselling in the eye clinic (Network 1000 Wave 2, 2008).
- A survey of individuals registered blind and partially sighted in the past eight years reveals that only 15% of them were offered any form of emotional support in the year after registration (Network 1000 Wave 2, 2008).
- Excluding those who had been most recently registered (in the past 2.5 years) only 6% of surveyed blind and partially sighted individuals received emotional support in the preceding year.
- Research carried out by RNIB (Nelson, 1999) found that 83% of individuals surveyed who were attending eye clinics said that they had not been offered any emotional support from a professional resource.
- One third of older individuals with poor vision or registered blind report a 'good' quality of life, compared with two-thirds of those with good or excellent vision ('An investigation of the circumstances of older people

with sight loss: analysis of the English Longitudinal Study of Ageing. UCL research for Thomas Pocklington Trust, October 2006).

The Macular Society fully supports the UK Vision Strategy which was launched in April 2008. Strategic Outcome 2 - Priority Action 2.3 says: "Eye care and sight loss services should include emotional support as an integrated part of the service. Services such as counselling should be available to users and to those supporting them as soon as a potential problem is identified. Links to support networks should also be offered."

14. Miscellaneous

14.1 Audit

This is an important part of any Macular Service and should include audit of the referral pathway, number and frequency of injections, complications and visual outcomes. Normal audit principles and practice would be expected as for any clinical service.

It will be important to demonstrate that patients with wet macular degeneration are seen and treated promptly to ensure that maximum benefit from these expensive drugs is obtained.

14.2 Research

The Final appraisal determination from NICE, TA155, issued in 2008 and last modified in 2012, recommends that further research into the effectiveness of anti-VEGFs in exudative AMD could include studies:

- To clarify the relative clinical effectiveness and cost effectiveness of ranibizumab compared to bevacizumab.
- To investigate the long term effects of anti-VEGFs in patients with AMD, including effects on visual acuity, anatomical damage to the macula, quality of life and adverse events.

- To establish the appropriate duration and optimal treatment regimen in terms of frequency of injections.

14.3 Next Review Date: 2015

GLOSSARY

ADVS- The ADVS (The Activities of Daily Vision Scale) is a 20 item quality of life measurement questionnaire.

AMD- Age- related macular degeneration

ANCHOR- ANti- VEGF antibody for the treatment of predominantly classic CHORoidal neovascularisation in age- related macular degeneration study. A phase 3 active-treatment controlled trial of 2 years duration in 422 patients.

AREDS- Age- related eye disease study

ARVO- Annual Meeting of the Association for Research in Vision and Ophthalmology

AVMD- Adult vitelliform macular dystrophy

BCVA- Best Corrected Visual Acuity

CATT- Comparison of AMD Treatments Trials

CEE- Conjugated Equine Oestrogens

CNV- Choroidal neovascularization

CNVM- Choroidal neovascular membrane

CRA- Chorioretinal anastomosis

CSR- Central serous retinopathy

CS- Contrast sensitivity

DHA- docosahexaenoic acid

DVA- Distance visual acuity

DLTV- The Daily Living Tasks Dependent on Vision (DLTV) is a quality of life (QOL) questionnaire that was constructed to obtain estimates of self-reported ability to perform vision-related tasks in persons with visual impairment due to age-related macular degeneration (AMD).

ECLO- Eye Clinic Liaison Officer

EMEA- European Medicines Agency

EPA- eicosapentaenoic acid

Fab- Fragment antigen binding portion

FAZ- Foveal avascular zone

FD- Fourier Domain

FOCUS- A phase 1/2 randomised single- masked study of ranibizumab in combination with PDT + verteporfin in 162 patients with predominantly classic CNV.

FFA- Fundus fluorescein angiography

FA- Fluorescein angiography

FAF- Fundus autofluorescence

FPED- Fibrovascular pigment epithelial detachment

GA- Geographic atrophy

GLD- Greatest linear diameter

HOPE- The Heart Outcomes Prevention Evaluation Study

IPC- Idiopathic polypoidal choroidopathy

ICGA- Indocyanine green angiography

IVAN- A randomised controlled trial of alternative treatments to **I**nhibit **V**EGF in **A**ge-related choroidal **N**eovascularisation.

IVTA- intravitreal triamcinalone

LLIO- Late leakage of indeterminate origin

LOV- Local Optical Committee

LVQOL- low vision quality-of-life questionnaire (LVQOL)

MacDQoL- The MacDQoL is an individualized measure of the impact of macular degeneration (MD) on quality of life (QoL)

MACTEL- Macular telangiectasia

MAI- Philadelphia Geriatric Center Multilevel Assessment Instrument

MARINA- Minimally classic/occult trial of Anti- VEGF antibody ranibizumab in the treatment of Neovascular Age- related macular degeneration. A phase 3 randomised sham controlled trial in 716 patients.

MLVQ- Manchester low vision questionnaire.

MPSG- Macular photocoagulation study group

NEI-VFQ- National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), designed to measure vision-specific health-related quality of life on a scale of 0 to 100 (100 indicates best possible functioning).

NICE- National Institute of Health and Clinical Excellence

OCT- Optical coherence tomography

P- Progestin

PD- Pattern dystrophy

PED- Pigment epithelial detachment

PIER- A phase 3b, multicentre, randomised, double-masked, sham injection controlled study in 184 patients of the efficacy and safety of ranibizumab in

subjects with subfoveal choroidal neovascularisation with or without classic CNV secondary to age-related macular degeneration.

PrONTO- Prospective OCT imaging of (40) patients with Neovascular AMD Treated with IntraOcular Lucentis. Patients received monthly injections for three months and retreatment decisions were based on OCT results.

PROTECT- An open label mulicentre phase 2 Study assessing the safety of same day ranibizumab administered in conjunction with PDT in patients with occult or predominantly classic subfoveal CNV secondary to AMD.

QoL- Quality of Life

RADICAL- this study is looking at the combination of PDT + ranibizumab+ dexamethasone

RAP- Retinal angiomatous proliferation.

RPE- Retinal pigment epithelium.

SAILOR- A phase 3b, multicentre study to evaluate the safety and tolerability of ranibizumab in naïve and previously treated subjects (n=5000) with CNV secondary to AMD.

SLO- Scanning laser ophthalmoscope

SNP- Single nucleotides polymorphisms

SUMMIT- these trials consist of the Denali (US) and Mont Blanc (Europe) looking at the safety and efficacy of PDT and ranibizumab.

SUSTAIN- One year multicentre open label study in 542 patients with classic or occult CNV. Patients received intravitreal injections of ranibizumab 0.3mg once a month for 3 months followed by criteria-based re-treatment for a total of 12 months.

TAP - Treatment of Age-Related Macular Degeneration with Photodynamic Therapy.

TTT- transpupillary thermotherapy

VA- visual acuity

VCM1- Vision core module 1 (VCM1)

VEGF- Vascular Endothelial Growth Factor

VERITAS- Verteporfin Intravitreal Triamcinalone Acetonide Study

Verteporfin (Visudyne) - a drug used as a photsensitiser in conjunction with a non-thermal photodynamic (PDT) laser.

VF-14- The VF-14 is a health survey questionnaire designed specifically for ophthalmology. "VF" stands for Visual Function, and "14" refers to the 14 questions in the main section of the questionnaire.

VIO- Visudyne in Occult Choroidal Neovascularisation

VIP- AMD- Verteporfin in Photodynamic Therapy-AMD [VIP-AMD]

VIP-PM- Verteporfin in Pathological Myopia

VISION studies- VEGF inhibition study in ocular neovascularization

VPDT- Verteporfin in Photodynamic Therapy

VQoL- Vision Specific Quality of Life (**VQOL**) questionnaire

WARMGS- Wisconsin Age-Related Maculopathy Grading Scheme

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http://evslarchive.moorfields.nhs.uk/amd_docs_0607/ref3.pdf

Conflict of Interest

Chair. Professor Usha Chakravarthy. The Chair of this group has provided advice and acted as consultant to the following organisations; Pfizer, Allergan, Novartis, Jerini, Neovista and Oraya and accepted speaking engagements and honoraria on their behalf. The commercial relationships of the other members of the group have been declared to the Chair.

Useful Sources of Information

Ophthalmic Mutal Insurance Company- www.omic.com provides informed consent documents for a wide variety of ophthalmological procedures which can be modified if necessary.

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