**Essentials in Ophthalmology**
*Series Editor:* Arun D. Singh

Hendrik P.N. Scholl
Robert W. Massof
Sheila West *Editors*

# Ophthalmology and the Ageing Society

Springer

Essentials in Ophthalmology

Hendrik P.N. Scholl • Robert W. Massof
Sheila West
Editors

Arun D. Singh
Series Editor

# Ophthalmology and the Ageing Society

Springer

*Editors*
Hendrik P.N. Scholl
Wilmer Eye Institute
John Hopkins University
Baltimore, Maryland
USA

Sheila West
Wilmer Eye Institute, Dana Center
for Preventive Ophthalmology
John Hopkins University
Baltimore, Maryland
USA

Robert W. Massof
Lions Vision Research and Rehabilitation
Wilmer Ophthalmological Institute
John Hopkins University
Baltimore, Maryland
USA

*Series Editor*
Arun D. Singh
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, Ohio
USA

ISBN 978-3-642-36323-8 ISBN 978-3-642-36324-5 (eBook)
DOI 10.1007/978-3-642-36324-5
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013939843



Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

# Preface

The ageing of the world's population is one of the major achievements of modern society. By 2050, an estimated two billion people will be aged 60 years or over.

But ageing poses major challenges and this is especially true for the field of ophthalmology. In actual fact, the major eye diseases, age-related macular degeneration, glaucoma and cataract, predominantly affect the elderly.

The challenges of ophthalmology in the ageing society have not been addressed in a comprehensive way, although there are common denominators of the various eye diseases by which an elderly population is affected. This book provides such a comprehensive overview including epidemiology, risk factors, current treatment and prophylaxis, disability, co-morbidity and the impact on quality of life.

Experts in their respective fields provide state-of-the-art knowledge on the geriatric aspects of ophthalmology and thus may help to improve our management of this growing patient population.

We are grateful to all the contributors for their work in making this book possible, and we are also grateful to the editorial and production staff at Springer for their commitment to the publication of our book.

Special thanks go to our colleagues at the Wilmer Eye Institute, Johns Hopkins University School of Medicine. We are surrounded by excellence in the ophthalmic field including research, teaching and patient care. We have the privilege to work at a unique place where cutting-edge research is being performed addressing many of the issues covered in this book – within the field of ophthalmology and beyond. The constant exchange of knowledge and ideas has very much stimulated the idea to publish on the subject and later the process of working on this book and strongly contributed to its quality.

Baltimore, Maryland

Hendrik P.N. Scholl
Robert W. Massof
Sheila K. West

# Contents

# Ophthalmic Disease in the Ageing Society

1

Emily C. Fletcher and Hendrik P.N. Scholl

## 1.1 Introduction

The diverse range of ophthalmic disease covers every ocular structure, function, ethnic group, mode of inheritance and of course every age range. Certainly, in the developed world, a significant proportion of disease is multifactorial in origin; however, in a large majority of cases, the underlying risk includes that of increasing age. Indeed, by 80 years old, more than 80 % of the main causes of blindness are due to age-related conditions such as cataract, glaucoma and age-related macular degeneration (AMD) (Finger et al. 2011b) (Fig. 1.1).

As a result, the impact of our growing elderly population has led to expansion of resource allocation for screening, treatment and monitoring of these potentially blinding conditions.

Epidemiological studies in AMD such as the Rotterdam, Blue Mountains and Beaver Dam Eye studies have provided prevalence data (Fig. 1.2) which identifies a sixfold risk of developing AMD at the age of 70–79, increasing to 25-fold in those over 80 in comparison to the 55–69 age range (Smith et al. 2001). Other factors such as smoking and genetic susceptibility are also associated with increased risk, however none as profound as increasing age. The growth of research into the subject of ageing as an entity has boomed in recent years boosted by the suggestion of genetic aetiology.

## 1.2 History of Ageing

Senescence, the biological deterioration with age, is thought to be an inevitable process in human development. In 1882 the evolutionary biologist August Weismann (Ljubuncic and Reznick 2009) theorized that ageing was a result of programmed cell death ensuing a limited number of somatic cell divisions, affording it a limited lifespan. The evolutionary benefit of a limited lifespan was thought to pertain to prevention of competition for food and space with younger individuals, who are still in their reproductive prime. In this circumstance, it was recognized that the process of reproduction is an essential requirement in order to maintain the species in a population that ages and degrades. As such, reproduction and fertility were concluded to be a greater factor in the evolutionary drive, and as in nature most animals did not reach old age, his theories were initially disregarded. Not until the 1950s did the ageing debate resurface, producing three key theories on the evolution of ageing:

E.C. Fletcher
Wilmer Eye Institute, Johns Hopkins University,
1800 Orleans Street, Baltimore,
Maryland 21287, USA

Gloucester Royal NHS Foundation Trust,
Gloucester Royal Hospital,
Great Western Way,
Gloucester, GL1 3NN, UK
e-mail: emily.fletcher@glos.nhs.uk

H.P.N. Scholl (✉)
Wilmer Eye Institute, Johns Hopkins University,
1800 Orleans Street, Baltimore,
Maryland 21287, USA
e-mail: hscholl1@jhmi.edu

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_1, 

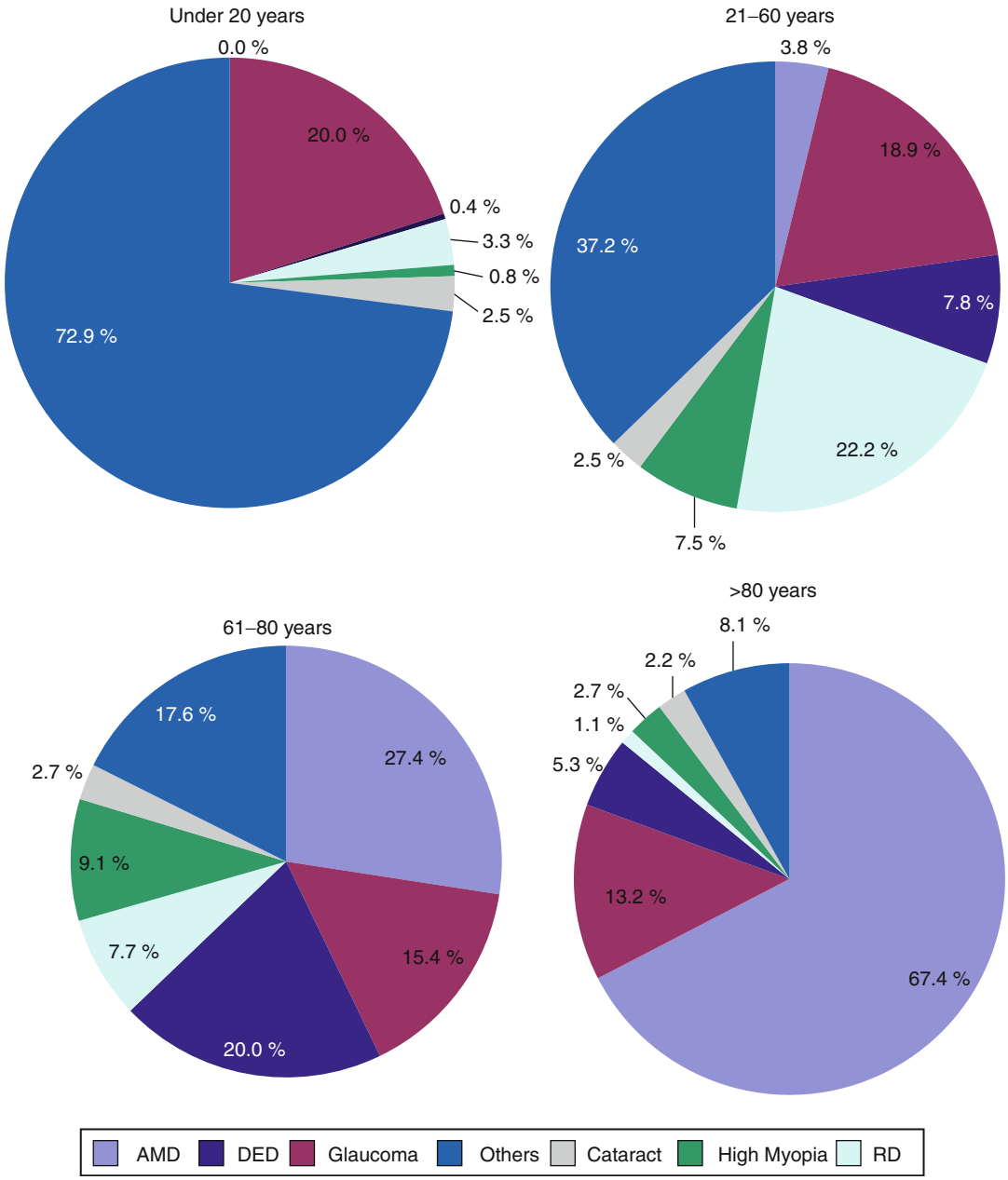


**Fig. 1.1** Prevalence rates shown as a percentage of total for the main causes of blindness and severe sight impairment in a German population

mutation accumulation, antagonistic pleiotropy and the disposable soma theory.

In 1952 *mutation accumulation* was described by Nobel Prize winner Peter Medawar (better known for his work on tissue transplantation), namely, ageing to be due to the random accumulation of detrimental mutations, which only become evident later in life, once the accumulation has reached a threshold. This effect would be outside the influence of evolution as natural selection can only exert its effect via the reproductive cycle. Therefore, as these traits only become evident after the

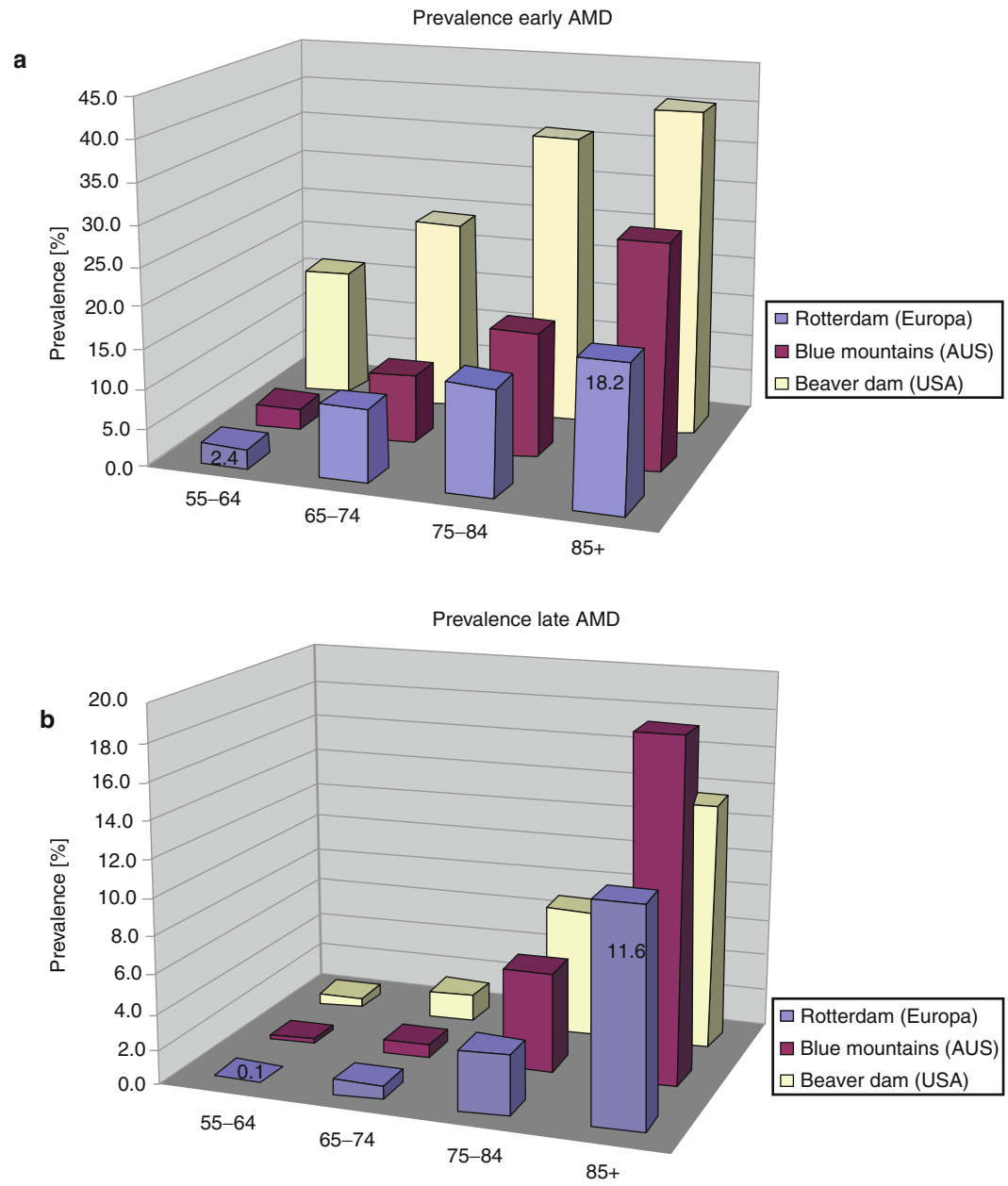


**Fig. 1.2** Prevalence data for early and late age-related macular degeneration from three epidemiological studies in Europe, Australia and the USA (Klein et al. 1992; Mitchell et al. 1995; Vingerling et al. 1995) (From Scholl et al. 2009)

reproductive prime, it was seen as a modification to Darwin's theory that the length of lifespan conveyed some form of advantage, as yet unknown.

*Antagonistic pleiotropy* (Tabatabaie et al. 2011) was proposed by George C. Williams in 1957 and has been further explored as the reproductive-cell cycle theory by Bowen and Atwood (Atwood and Bowen 2011). He discussed the possibility that one gene could be responsible for two traits: one beneficial, responsible for fertility, and one detrimental, responsible for ageing. This necessitated a "fitness trade-off". In order to have the desired trait of fertility, senescence was always present. Evidence for the link between fertility and longevity is

seen in many animals and recently has been demonstrated in humans (Tabatabaie et al. 2011). It also provides a connection between senescence and natural selection. Expanding the *trade-off* theory was Thomas Kirkwood (1977) who proposed the *disposable soma theory* (Kirkwood 1977; Kirkwood 2002). This described a limited energy input with the need to ration what it was then used for reproduction, repair or maintenance. The compromise of the accuracy in the repair function in favour of reproduction inevitably leads to an accumulation of damage and resultant ageing.

The complex interplay between genetics and environment is borne out in the fact that longevity genes are thought to account for only 20–30 % of senescence (Hjelmborg et al. 2006). The instigation of the Genetics of Healthy Ageing (GEHA) project (Skytthe et al. 2011) was established in order to identify the longevity genes and those involved in healthy ageing and the underlying processes they control which may allow a better understanding of the environmental influence.

In the field of ophthalmology, we see several ways in which these theories are borne out where several diseases only appear in old age, specifically age-related macular degeneration, which has an influence from genetics which are not specific to the eye, a significant influence from increased vulnerability due to wear and tear and the complexity of environmental modifiable factors.

## 1.3 Maximum Life Expectancy

All of these aforementioned theories, however, focus on the idea of a finite lifespan. The predicted maximum life expectancy has had to be re-calculated several times over the past 80 years. During the 1920s, the maximum age was 57 years. At that time, Louis Dublin made an estimation that the maximum life expectancy would rise to 64.75 years, using available data from the USA at that time. Unbeknown to him, this level had already been exceeded by the female non-Maori population in New Zealand, 7 years previously. Estimation of maximum longevity requires analysis of collected mortality data in order to determine trends. This data was then and in many areas still is not a comprehensive data set. As a result, Fig. 1.3 demonstrates the number of estimates which have been exceeded during this period.

Interestingly, despite the fact that this trend in longevity has occurred as a result of significant extrinsic improvements to the environment around us (such as advancement in health and safety, nutrition, medical treatments, the reduction in infant mortality and sanitation), the graph produces a very linear progressive delay in mortality. The life expectancy 200 years ago was 40 years of age with a steady increase in best practice life expectancy[1] of 3 months per year in females for the past 160 years (Oeppen and Vaupel 2002) (Fig. 1.3) with the example of Japanese women now having a life expectancy of over 85 years.

As identified in the above chart, this continued increase in life expectancy does not appear to be levelling off or reaching its peak. We have seen that the probability of an 80-year-old living to the age of 90 has increased in 1950–2002 from 15 to 37 % for women and 12 to 25 % for men. It is expected that if this rate of increase continues persons born in the year 2000 in developed European countries, the USA and Japan can expect to live to see their 100th birthday (Fig. 1.4).

Concern is mounting that alongside increasing age and senescence comes vulnerability and therefore increased susceptibility to ill health and disability. An increasingly aged population could potentially result in additional social and economic burden. This measure is less definite than mortality rates due to the mode of collection and subjectivity of the data. Investigation shows that the prevalence of morbidity in the aged population has increased, possibly due to increased reporting and earlier diagnosis and a more health conscious population along with a reduced mortality rate. However, research suggests that included in the postponement of mortality seems to be a delay in disability, allowing a healthier old age rather than a prolongation of disability and vulnerability. The measurement of

[1]Best practice life expectancy is the highest life expectancy achieved in that year.

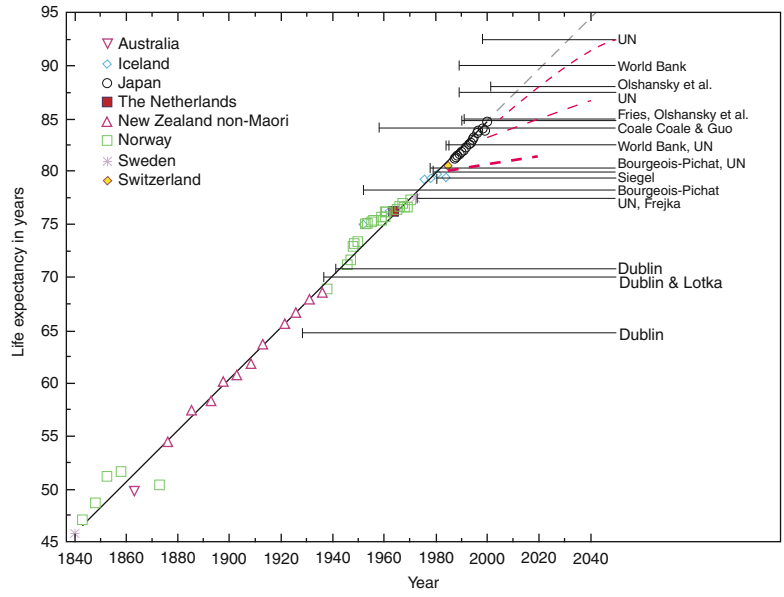


**Fig. 1.3** Record female life expectancy from 1840 to present day. The linear regression trend is depicted by a *bold black line* (slope = 0.243) and the extrapolated trend by a *dashed grey line*. The *horizontal black lines* show asserted ceilings on life expectancy, with a *short vertical line* in dictating the year of publication. The *dashed red lines* denote projections of female life expectancy in Japan published by the United Nations in 1986, 1999 and 2001 (Oeppen and Vaupel 2002)

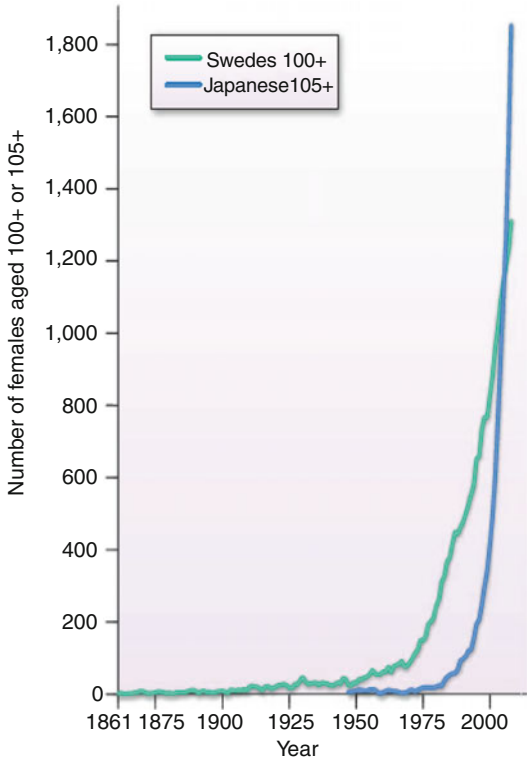


**Fig. 1.4** This graph depicts the extensive rise in centenarians in Sweden and Japan from 1861 to 2000 (Vaupel 2010)

the rate of disability within this increased morbidity adds additional complexity in measurement. The presence of disease, especially if it is detected earlier and treated in a timely fashion, does not always lead to increased disability.

The measure of disability-free life expectancy (DFLE) includes both the mortality and disability data, thus allowing identification as to whether increased life expectancy is spent in good or ill health. There is limited longitudinal data looking at the transition from good heath to disease with the progression to disability and eventual death. In looking at the impact a disease has on a person, you would need to assess both the total life expectancy (TLE) and also the DFLE. This would allow better insight into the quality of the remaining life. TLE for men at the age of 65 is 15.3 years, of which 12.1 years were disability-free (Jagger et al. 2007). For women aged 65, the TLE is 19.4 years, but only 11.0 years are disability-free. The most significant disease-specific impact on life expectancy is not unsurprisingly from stroke and diabetes resulting in a TLE of 4.4–5.6 years at the age of 65. Visual impairment, however, does not impact TLE (Jagger et al. 2007) and has a much greater impact on mild rather

than moderate disability. In addition, the rate of DFLE in visual impairment is increasing at a faster rate than TLE. This means that any disability that arises is compressed into a shorter period of their remaining life. It is also evident that modifiable life factors such as smoking and nutrition have a greater impact on reducing morbidity than mortality. This would help to explain the increased DFLE and reiterates the impact of lifestyle education.

This aspect has a great impact on the provision of social and health care in view of not only the increasing size of the population in general but in particular the increase in the proportion of aged. The recent census in 2010 showed population increase in the United states alone of 9.7 % from the year 2000 to 2010 resulting in a population of 308.7 million (Mackun and Wilson 2011). Although this was less of an increase than the previous 10 years, the population has been steadily increasing since the 1900s. The age distribution showed that the 45–64 age group comprised 81.5 million (26.5 %) and the over 65 age group comprised of 40.3 million people (13.0 %) with an increase of 31.5 and 15.1 %, respectively. This proportional increase in the older generation is significantly higher than the younger age group and is partially due to the baby boom following World War II. A similar pattern of increase is seen in the Japanese and European populations (Fig. 1.5).

The pyramids in Fig. 1.5 show the different patterns of population distribution. All populations show an increased mean age with time, as the widest part of the pyramid shifts towards older age, alongside variability in the absolute mean age between countries. The population of Japan shows population contraction, in comparison to an underdeveloped country such as Kenya which shows population expansion. The population pyramid also shows the delay in mortality as described earlier.

Demographic data from a German population shows the shape of the population curve remains unchanged between 2005 and 2025 (Fig. 1.6a); however, there is a predicted shift to the right. This 20-year shift is attributed to changes in mortality rates rather than immigration flux.

The implication of longevity alongside the shift in the population size and age distribution requires provision for the economic impact of the health and social demands. In this context, the impact of age-related diseases and ocular health and vision requires re-evaluation. The estimate for the total financial cost of visual impairment in those aged over 40 years in the USA was $35.4 billion (Rein et al. 2006). A significant proportion of this was from AMD and cataract, which naturally predominate in the ≥65 age group. It is seen that the overall reduction in visual acuity over a 10-year period is 3–4 letters in people between 55 and 64 years of age. This increases to 11–12 letters in those over the age of 75 years (Klein et al. 2001). The 10-year incidence of severe visual impairment in the general population of the Beaver Dam Eye Study was 0.8 %, increasing to 5.6 % in the over 75-year-olds (Klein et al. 2001). In view of the treatment options for exudative age-related macular degeneration, this may have altered to a small degree since the study was completed. However, despite this, there is a significant proportion of the aged population that require medical and social attention often leading to secondary consequences such as falls, depression, isolation or requirement for nursing homes.

## 1.4 Meeting the Challenges Ahead

The knowledge of this trend has prompted predictions regarding the level of blindness and severe vision impairment to facilitate future health-care planning. Predicted increased levels of blindness and severe visual impairment following collection of large data sets from welfare institutions in Germany (Fig. 1.6) (Finger et al. 2011b) are thought to be largely as a result of AMD, requiring any adjustment in health-care provision to be cognizant of these shifts in disease and age patterns. We have recently been able to observe just how such adjustments in increased research and provision for age-related eye disease

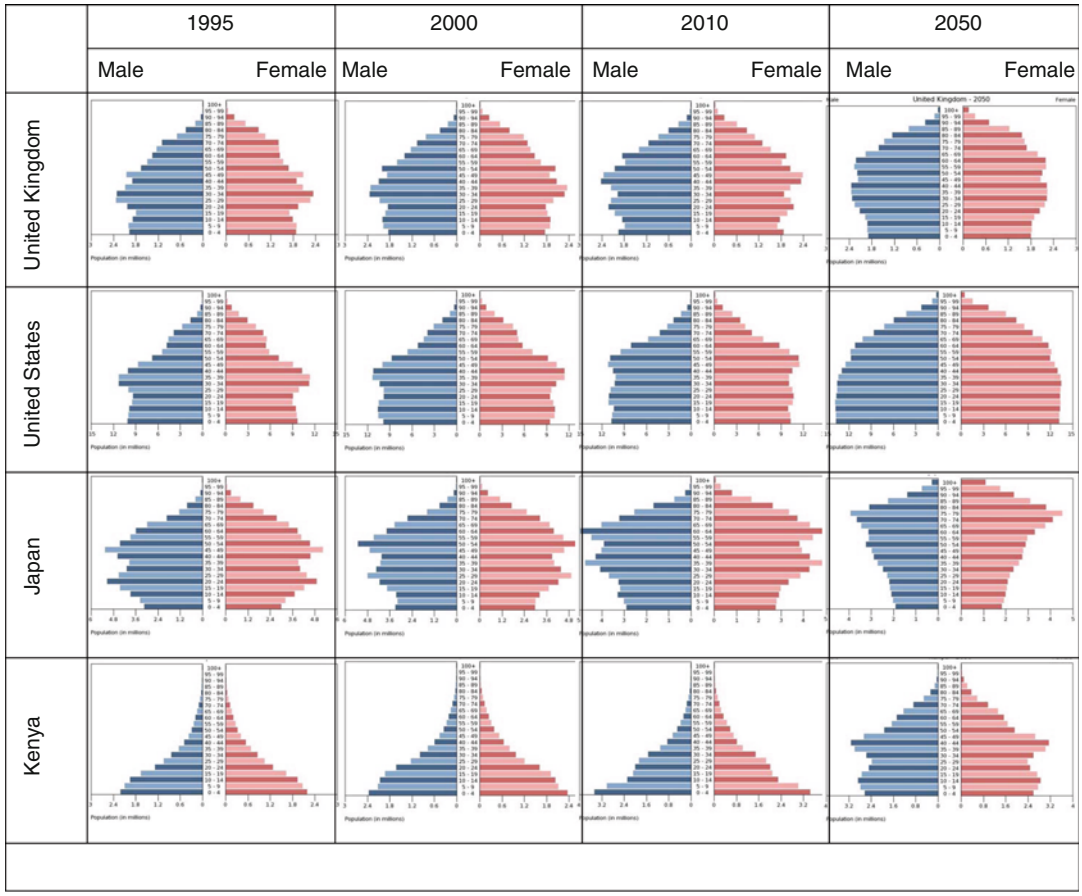


**Fig. 1.5** Population pyramids for developed and underdeveloped countries. *Blue* figure depicts the male population and *pink* the female population over the years from 1995 to 2010 with prediction for 2050

are now beginning to bear fruit. Recent publications provide evidence of *decreasing* incidence of blindness in certain areas (Bressler et al. 2011; Bloch et al. 2012; Skaat et al. 2012). Predominantly as a result of the advent of anti-VEGF treatments for exudative AMD, this has helped to reduce the level of legal blindness, in comparison to the figures 10 years previously.

This observed fall in blindness however is not solely due to the treatment effect – although there was a significant change seen in 2006 which would fit with the anti-VEGF timeline, but also as a result of increased awareness, established screening programmes and earlier detection. The change in the public health awareness has certainly proven a great success in the prevention of severe disease in cases such as glaucoma and diabetic eye disease. Fortunately, the elderly population are active information seekers as regards their health and nutrition. Access to resources in a variety of formats is seen to be "enabling" leading to an enhanced perception of control and power over one's well-being. This empowerment has led to the further understanding and alteration in many of the potential modifiable risk factors to enable this population to not only improve their longevity but participate in good health without disability or visual impairment.

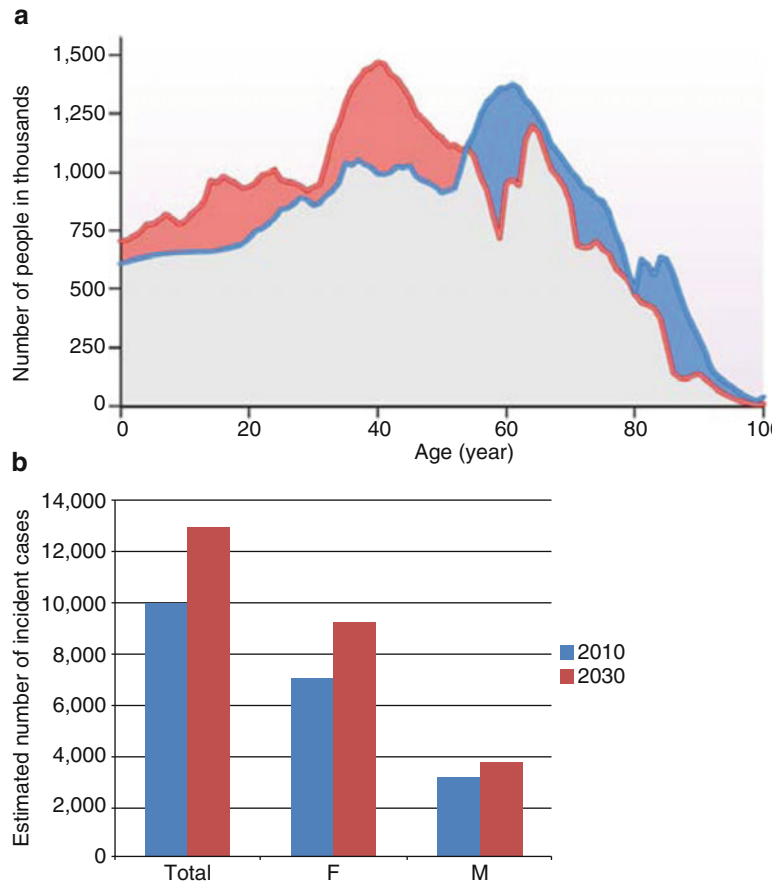


**Fig. 1.6** (**a**) German population distribution by age. The population age distribution in 2005 (*red line*) and the projected population in 2025 (*blue line*) (Data from Human Mortality Database Vaupel 2010). (**b**) Total and predicted cases of blindness and severe visual impairment for Germany in 2010 (*Blue*) and 2030 (*Red*) (Finger et al. 2011a)

**Acknowledgments** Conflict of interest: none; Ethical standards: informed consent – not applicable; Animal rights – not applicable.

## References

Atwood CS, Bowen RL (2011) The reproductive-cell cycle theory of aging: an update. Exp Gerontol 46(2–3):100–107

Bloch SB, Larsen M et al (2012) Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. Am J Ophthalmol 153(2):209–213.e202

Bressler NM, Doan QV et al (2011) Estimated cases of legal blindness and visual impairment avoided using Ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. Arch Ophthalmol 129(6):709–717

Finger RP, Fimmers R et al (2011a) Incidence of blindness and severe visual impairment in Germany: projections for 2030. Invest Ophthalmol Vis Sci 52(7):4381–4389

Finger RP, Fimmers R et al (2011b) Prevalence and causes of registered blindness in the largest federal state of Germany. Br J Ophthalmol 95(8):1061–1067

Group DE (2010) Commission staff working document. Demography report 2010

Hjelmborg J, Iachine I et al (2006) Genetic influence on human lifespan and longevity. Hum Genet 119(3):312–321

Jagger C, Matthews R et al (2007) The burden of diseases on disability-free life expectancy in later life. J Gerontol A Biol Sci Med Sci 62(4):408–414

Kirkwood TB (1977) Evolution of ageing. Nature 270(5635):301–304

Kirkwood TB (2002) Evolution of ageing. Mech Ageing Dev 123(7):737–745

Klein R, Klein BE et al (1992) Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 99(6):933–943

Klein R, Klein BE et al (2001) Changes in visual acuity in a population over a 10-year period: The Beaver Dam Eye Study. Ophthalmology 108(10): 1757–1766

Ljubuncic P, Reznick AZ (2009) The evolutionary theories of aging revisited – a mini-review. Gerontology 55(2):205–216

Mackun P, Wilson S (2011) Population distribution and change: 2000 to 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-01.pdf. Accessed on 2 Mar 2013

Mitchell P, Smith W et al (1995) Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. Ophthalmology 102(10):1450–1460

Oeppen J, Vaupel JW (2002) Demography. Broken limits to life expectancy. Science 296(5570):1029–1031

Rein DB, Zhang P et al (2006) The economic burden of major adult visual disorders in the United States. Arch Ophthalmol 124(12):1754–1760

Scholl HPN, Charbel Issa P, Fleckenstein M, Schmitz-Valckenberg S, Holz FG (2009) Age-related macular degeneration. In: von Lang F (ed) Encyclopedia of molecular mechanisms of disease. Springer, Berlin/Heidelberg/New York, pp 1244–1247

Skaat A, Chetrit A et al (2012) Time trends in the incidence and causes of blindness in Israel. Am J Ophthalmol 153(2):214–221.e211

Skytthe A, Valensin S et al (2011) Design, recruitment, logistics, and data management of the GEHA (Genetics of Healthy Ageing) project. Exp Gerontol 46(11):934–945

Smith W, Assink J et al (2001) Risk factors for age-related macular degeneration: pooled findings from three continents. Ophthalmology 108(4):697–704

Tabatabaie V, Atzmon G et al (2011) Exceptional longevity is associated with decreased reproduction. Aging (Albany NY) 3(12):1202–1205

U.S. Census Bureau International Database. http://www.census.gov/population/international/data/idb/informationGateway.php. Accessed on 2 Mar 2013

Vaupel JW (2010) Biodemography of human ageing. Nature 464(7288):536–542

Vingerling JR, Dielemans I et al (1995) The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 102(2):205–210

# Part I

# Epidemiology of Eye Diseases in Older Populations

# Blindness and Visual Impairment: Global Perspective

2

Sheila K. West

## 2.1 Introduction

The last 30 years have seen a dramatic shift in global economies and a rise in the number and wealth of so-called "middle-income" countries. Notwithstanding the terrible toll of HIV-AIDS, survival rates have generally improved and with it an increase in the proportion of deaths due to chronic diseases as the infectious diseases decline (World Health Organization 2011). The World Health Organization (WHO) now has to face a rising epidemic of illnesses like diabetes as seriously as it has faced epidemics of infections like cholera or yellow fever (World Health Organization 2011).

## 2.2 Burden of Blindness

This global change in the rise of chronic diseases is also mirrored in the shift in causes of blindness and visual loss from anterior, infectious causes to posterior, chronic causes. One of the first articles from the prevention of blindness office of WHO in 1972 described an overall estimate of blindness worldwide of 15 million persons (World Health Organization 1973). Blindness was defined as best-corrected visual acuity of worse than 3/60 or 20/400. An update by WHO in 1990 reported about 38 million blind persons (Thylefors et al. 1995) and suggested that the number of visually impaired was 2.9 times as great or 110 million. In the 2004 publication, the estimate was 37 million with an estimated additional 124 million persons with severe visual impairment, defined as vision worse than 20/60 but not blind (Resnikoff et al. 2008). However, with the addition of uncorrected refractive error, the estimate for numbers of blind persons increased to 45 million and 269 million with low vision. By 2010, the estimate of the number of blind worldwide was 39 million (3 % due to refractive error) with 246 visually impaired. Of the visual impaired group, 43 % was estimated due to refractive error and 33 % due to cataract (Pascolini and Mariotti 2012). Figure 2.1 shows the estimates of blindness (not due to refractive error as earlier reports did not include refractive error) over time. Despite a population growth in the 20 years since 1990, it does not appear that the number of blind persons has increased since that time and certainly not to the dire level originally predicted. There is clearly some caution warranted in the size of errors with these numbers, depending as they do on some interpolation and "guess estimates" where data were not available.

S.K. West, PhD
Dana Center for Preventive Ophthalmology,
Wilmer Eye Institute, Johns Hopkins University
School of Medicine, Baltimore, MD, USA
e-mail: shwest@jhmi.edu

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_2, © Springer-Verlag Berlin Heidelberg 2013

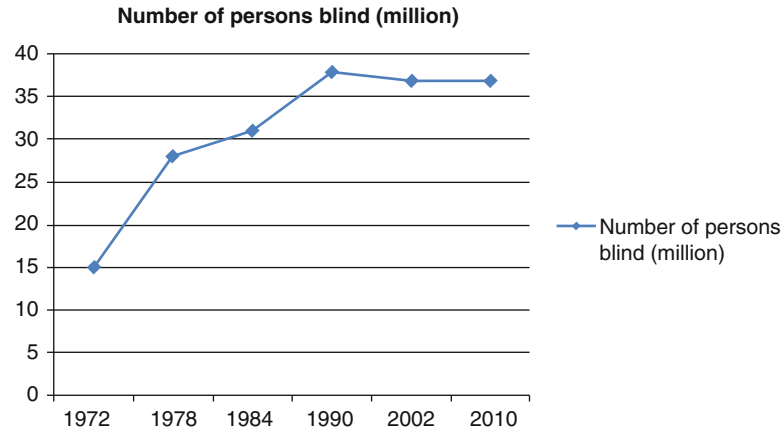


**Fig. 2.1** Estimate of number of persons blind (excluding refractive error) worldwide over time

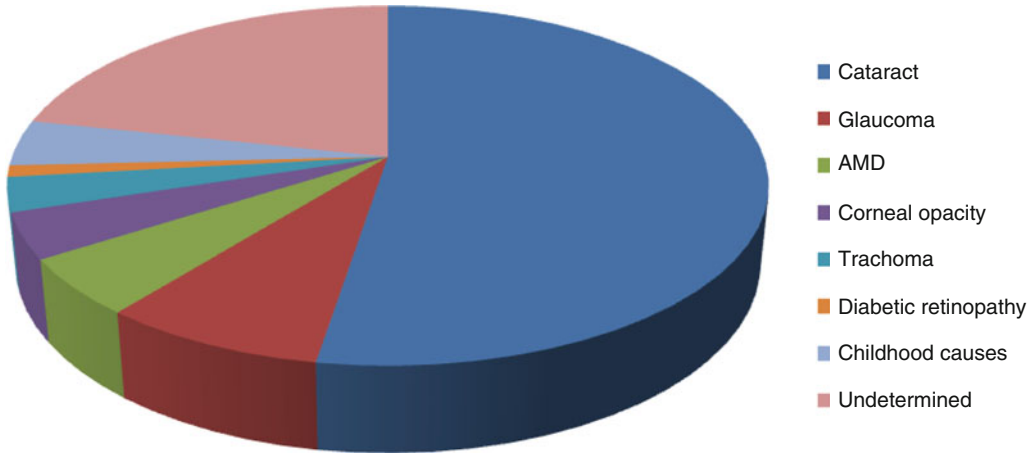


**Fig. 2.2** Causes of blindness 2010 (Pascolini and Mariotti 2012)

## 2.3 Causes of Blindness

The leading causes of blindness in 1990 were cataract, trachoma, and glaucoma (Thylefors et al. 1995). By 2002, the leading cause of blindness was still cataract (47 %), but followed by chronic eye diseases: glaucoma (12 %), age-related macular degeneration (9 %), and diabetic retinopathy (5 %) (Resnikoff et al. 2004). Trachoma was reported to be the fifth cause of blindness worldwide, tied with childhood blindness from all causes, and onchocerciasis was the cause for less than 1 %. Current data on causes of blindness continue to mirror the rise in age-related diseases (Fig. 2.2). An estimated 80 % of all visual loss can be prevented or cured, most of this being due to cataract.

To the casual observer, the persistence of cataract as a leading cause of vision loss is puzzling. The threshold for performing cataract surgery has gotten less stringent over time, reflecting better postoperative outcomes and demand by patients for improved functional abilities at increasingly less severe levels of cataract. In many high-income countries, like Denmark and the UK, the number of cataract operations has doubled or trebled over time (Williams and Seward 1993; Norregaard et al. 1996). With surgery such an effective intervention and demand seemingly increasing, why is vision loss due to cataract still so prevalent? In part, the answer lies in a further statistic: the burden of blindness is not equitable, with 90 % in low-income countries

(http://www.who.int/mediacentre/factsheets/fs282/en/). As Brian and Taylor describe, lack of cataract surgical services result from a complex mix of cultural issues around access combined with too few cataract surgeons and/or maldistribution of surgeons and lack of equipment and supplies (Brian and Taylor 2001). Reports from Nigeria still describe cataract treated with couching, an archaic procedure where the lens is literally pushed down into the vitreous (Gilbert et al. 2010). Moreover, where conventional surgery is available, the quality of outcomes can be poor. Models for providing high-volume, cost-effective, high-quality outcome cataract services exist, notably Aravind Eye Hospital in India (Natchiar et al. 1994). The population density and high need are important features of that model and make translation to many African settings, where 80 % or more of the population are scattered in rural settings, more challenging.

Until relatively recently, the problem of uncorrected refractive error was not recognized. The definition of blindness or vision loss was based on the results of testing using best correction, thus effectively ignoring refractive error. With the growing realization that myopia was becoming an epidemic in parts of the world, literally within a generation or two, the magnitude of uncorrected refractive error as a cause of visual loss became important to measure. Now, the testing for visual impairment surveys is often done with the use of available spectacles. At present, the World Health Organization reports 19 million children worldwide are visually impaired and 17 of these are due to refractive error (http://www.who.int/mediacentre/factsheets/fs282/en/). The reasons for lack of cost-efficient refractive services share similarities with the reasons for lack of cataract surgical services, including lack of appropriate human resources, and lack of optical products. There is also the added problem in children of biases against wearing spectacles. A review article recommended school-based screening approaches, which appear to work if school attendance is high and not disparate by socioeconomic status or gender (Sharma et al. 2012). However, much of the professed need for spectacles is in the older age groups where reading glasses would improve quality of life. Even in rural Africa, the provision of reading spectacles to those with presbyopia resulted in an improvement in ability to carry out daily activities and a willingness to pay for spectacles (Patel et al. 2010). There are some imaginative solutions to provision of ready-made reading spectacles to low-income countries, using an interesting entrepreneurial model that promotes social development (William Davidson 2008).

Besides cataract, the other age-related eye diseases of public health significance are glaucoma and age-related macular degeneration. There is no proven preventive strategy for either of these two diseases, so once diagnosed, various treatment options are necessary to avoid or delay progression. Quigley and Broman estimated the number of persons with glaucoma worldwide as about 60 million, most of whom will have open-angle glaucoma (Quigley and Broman 2006). Persons of Asian descent are at greater risk of angle-closure glaucoma compared to Caucasians. In the USA, African Americans and Latinos appear to have higher rates of glaucoma and blindness from glaucoma (Friedman et al. 2004). Glaucoma has long been the "elephant in the room" in the blindness prevention community because it is felt to be cumbersome to diagnose and treatment options for low-income countries are not straightforward. Therefore, prevention of blindness from glaucoma has not been a major feature of WHO or International Agency for Prevention of Blindness (IAPB) activities, although this is now the second leading cause of best-corrected blindness. One barrier has been the decision on the need for visual function testing, routine for high-income countries, as part of the diagnosis of glaucoma. A recent report evaluating the assessment of visual function in glaucoma noted that technology advances and analytic tools have resulted in more rapid testing but concluded that the tests have not provided any definitive answer to diagnosis or measurement of progression over time (Jampel et al. 2011).

Age-related macular degeneration (AMD) is a leading cause of visual loss among older Caucasians. The "wet" form of AMD (CNV), while less common than the "dry" form, can be

catastrophic for central vision as abnormal blood vessels start to grow under the macula. Various forms of laser treatment were used to delay vision loss, and one clinical trial suggested that use of a combination of zinc and antioxidant multivitamins may delay progression to CNV in a subset of patients with a particular form of early AMD (Age-Related Eye Disease Study Research Group 2001). With the finding that abnormally high levels of vascular growth factors are secreted in eyes with CNV came new treatment strategies targeting these growth factors. A recent clinical trial in patients with AMD demonstrated the equivalence of two forms of commercially available anti-vascular endothelial growth factor, one considerably less expensive than the other (CATT Research Group et al. 2011). Nevertheless, from a public health perspective, it requires a specialist to diagnose AMD and certainly to provide any of the treatment options at the present time which makes the management of AMD out of the reach of most low-income countries. Smoking has been strongly linked to severe AMD, although not consistently to the precursor lesions, suggesting that smoking avoidance and quitting smoking, as part of an approach to improving general health, should have beneficial effects on reduction of risk of AMD in susceptible populations.

## 2.4 Global Initiatives to Eliminate Blindness

Vision 2020: The Right to Sight is the global initiative to eliminate avoidable blindness by the year 2020. The strategic aim now is advocacy, to give eye care greater priority in national budgets and health policy, and integrate eye care services into health systems. There are compelling reasons to further this agenda. A recent article has estimated the total global cost of visual impairment at $3 trillion in 2010, of which $2.3 trillion was directly related to health-care costs and the other costs related to indirect factors such as reduced productivity and informal care costs (Gordois et al. 2012). While the estimate of persons with blindness was much higher than other published reports (156 million), if even a conservative estimate is 1/3 of these costs, they represent a substantial burden. Uncorrected refractive error was 54 % of the financial cost ($1.6 trillion) and AMD was 12 % (0.3 trillion). The authors projected the burden to increase by 20 % by 2020, based on projections of increasing burden of disease with population growth. The fact that projections of increasing burden of numbers of visually impaired in the past have not materialized, despite growth in the aging population, is reason to be hopeful that blindness prevention programs are working. Of note, though, some researchers attribute this lack of increase in blindness to the success of onchocerciasis and trachoma control programs which have decreased infectious causes of blindness worldwide. As we continue in an era where age-related, chronic eye diseases will dominate the eye health landscape, it remains to be seen if strides in reduction of visual impairment can persist. As the majority of cases of visual impairment reside inequitably in the less advantaged countries, such strides must consider strategies appropriate to prevention, screening, and treatment in those settings.

**Acknowledgments** Conflict of Interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Age-Related Eye Disease Study Research Group (2001) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. Arch Ophthalmol 119: 1417–1436

Brian G, Taylor HR (2001) Cataract blindness-challenges for the 21st century. Bull World Health Organ 79(3): 249–256

CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 364: 1897–1908

Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, Leske MC, Mitchell P, Congdon N, Kempen J (2004) Eye Diseases Prevalence Research Group. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol 122: 532–538

Gilbert CE, Murthy GV, Sivasubramaniam S, Kyari F, Imam A, Rabiu MM, Abdull M, Tafida A (2010) Couching in Nigeria: prevalence, risk factors and visual acuity outcomes. Ophthalmic Epidemiol 17(5): 269–275

Gordois A, Cutler H, Pezzulo L, Gordon K, Cruess A, Winyard S, Hamilton W, Chua K (2012) An estimation of the worldwide economic and health burden of the visual impairment. Glob Public Health 7:465–481. doi:10.1080/17441692.2011.634815

http://www.who.int/mediacentre/factsheets/fs282/en/. Accessed on April 10, 2012

Jampel HD, Singh K, Lin SC, Chen TC, Francis BA, Hodapp E, Samples JR, Smith SD (2011) Assessment of visual function in glaucoma: a report by the American Academy of Ophthalmology. Ophthalmology 118:986–1002

Natchiar G, Robin AL, Thulasiraj RD, Krishnaswamy S (1994) Attacking the backlog of India's curable blind. The Aravind Eye Hospital model. Arch Ophthalmol 112:987–993

Norregaard JC, Bernth-Petersen P, Andersen TF (1996) Changing threshold for cataract surgery in Denmark between 1980 and 1992. Acta Ophthalmol Scand 74:604–608

Pascolini D, Mariotti SP (2012) Global estimates of visual impairment: 2010. Br J Ophthalmol 96:614–618

Patel I, Munoz B, Mkocha H, Schwarzwalder AW, Mchiwa W, West SK (2010) Change in function and spectacle-use 2 months after providing presbyopic spectacles in rural Tanzania. Br J Ophthalmol 94: 685–689

Quigley HA, Broman AT (2006) The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 90:262–267

Resnikoff S, Pascolini D, Etyaale D, Kocur I et al (2004) Global data on visual impairment in the year 2002. Bull World Health Organ 82:844–851

Resnikoff S, Pascolinin D, Mariotti SP, Pokhrel GP (2008) Magnitude of visual impairment caused by uncorrected refractive error in 2004. Bull World Health Organ 86:63–70

Sharma A, Congdon N, Patel M, Gilbert C (2012) School-based approaches to the correction of refractive error in children. Surv Ophthalmol 57:272–283

Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY (1995) Global data on blindness. Bull World Health Organ 73:115–121

William Davidson Institute (2008) Case 1-428-610. ScoJo Foundation: a vision for growth at the base of the pyramid. 18 Apr 2008. Ross School of Business, University of Michigan. www.wdi.umich.edu. Accessed on April 10, 2012

Williams ES, Seward HC (1993) Cataract surgery in South West Thames Region: an analysis of age-adjusted surgery rates and length of stay by district. Public Health 107:441–449

World Health Organization (1973) The prevention of blindness. Report of a WHO study group. WHO technical report series no 518. World Health Organization, Geneva

World Health Organization (2011) Global status report on noncommunicable diseases 2010. World Health Organization, Geneva, pp 1–76

# Blindness and Visual Impairment: High-Income Countries

3

Robert P. Finger and Hendrik P.N. Scholl

## 3.1 Introduction

Patterns and prevalence of visual impairment and blindness in high-income countries including all of Western Europe, Northern America and Australia are distinctly different from global estimates. As outlined in the previous chapter, global visual impairment and blindness is mostly found in low- and middle-income countries and is mainly due to a number of potentially preventable and/or treatable causes (Pascolini and Mariotti 2012). In comparison, in high-income countries, the prevalence and incidence of visual impairment and blindness is much lower and mostly due to causes related to the ageing of the population. A number of the main causes of visual impairment and blindness in these countries are currently not amenable to prevention, and treatment can be unsatisfactory in that it may only slow down the progression of a number of these diseases, but does not cure them. The main disorders are complex diseases, with a genetic and an environmental component, with ageing being often the single most important factor in the aetiology. Unfortunately, as visual impairment and blindness is not perceived as a large public health issue in many high-income countries, population-based cohort studies are scarce with no published population-based data available. A recent publication of global estimates of visual impairment by the World Health Organization (WHO) highlighted this shortcoming once again. Only two studies, conducted in Russia and Turkmenistan, qualified for inclusion in the estimations for Europe (Pascolini and Mariotti 2012). However, the considerable impact of visual impairment not only on an individual's quality of life but also the substantial cost born by society merits significant research efforts and appropriate service provision in all high-income countries (Taylor et al. 2006; Porz et al. 2010). Not only does longevity continue to increase in all high-income countries but workplace requirements change rapidly as well. Visually impaired persons may often be particularly disadvantaged by these trends, in an economy driven increasingly by visual technology (West and Sommer 2001). Together with the age of retirement being up for discussion in a number of countries, this should create even more of an incentive for governments to invest into research and service provision in order to maintain lifelong good vision. In the following discussion, the prevalence and incidence estimates generated from a number of available population-based studies as well as similar estimates based on blind registers will be

R.P. Finger (✉)
Centre for Eye Research Australia,
Royal Victorian Eye and Ear Hospital,
University of Melbourne, Melbourne, VIC, Australia

Department of Ophthalmology,
University of Bonn, Bonn, Germany
e-mail: robert.finger@unimelb.edu.au

H.P.N. Scholl
Wilmer Eye Institute,
John Hopkins University, Baltimore, MD, USA

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_3, 

depicted, followed by a brief paragraph on visual impairment in the elderly and risk factors for blindness in high-income countries (which are discussed in more depth in Chaps. 4 and 5). Finally, currently available projections of future trends of visual impairment and blindness in high-income countries are discussed.

## 3.2 Magnitude of Visual Impairment and Blindness in the Elderly

Several population-based epidemiological studies are available to shed light onto the current magnitude of visual impairment and blindness in the elderly. Most of the data presented originates from the Beaver Dam Eye Study (BDES, USA), the Blue Mountains Eye Study (BMES, Australia), the Melbourne Visual Impairment Project (MVIP, Australia) and the Rotterdam Eye Study (RES, Netherlands).

**Table 3.1** Definition of blindness and low vision according to the International Classification of Diseases, 10th revision

| | Presenting distance visual acuity | |
|---|---|---|
| Category | Worse than | Equal to or better than |
| 0 Mild or no visual impairment | | 6/18<br>3/10 (0.3)<br>20/70 |
| 1 Moderate visual impairment | 6/18<br>3/10 (0.3)<br>20/70 | 6/60<br>1/10 (0.1)<br>20/200 |
| 2 Severe visual impairment | 6/60<br>1/10 (0.1)<br>20/200 | 3/60<br>1/20 (0.05)<br>20/400 |
| 3 Blindness | 3/60<br>1/20 (0.05)<br>20/400 | 1/60[a]<br>1/50 (0.02)<br>5/300 (20/1200) |
| 4 Blindness | 1/60[a]<br>1/50 (0.02)<br>5/300 (20/1200) | Light perception |
| 5 Blindness | No light perception | |

[a]Or count fingers (CF) at 1 m

### 3.2.1 Definition

Blindness and low vision are defined in various ways, depending on the legal or regulatory context of the definition. The most ubiquitous definition is laid out by the World Health Organization (WHO) in the International Classification of Diseases (ICD), 10th revision (Table 3.1) (World Health Organization 1990). The definitions in the ICD are based on best-corrected visual acuity. However, in order to reflect day-to-day impairment from low vision, most WHO studies and estimates are based on visual acuity measurements with habitual or presenting correction in order to reflect the considerable amount of blindness and visual impairment due to uncorrected or insufficiently corrected refractive errors. If the extent of the visual field is taken into account, patients with a visual field of the better eye no greater than 10° in radius around central fixation are placed in category 3.

Another very commonly encountered definition is the legal definition of blindness and low vision used in the USA. Best-corrected visual acuity in the better seeing eye of ≤20/200 or <20/40 defines blindness and low vision, respectively. Visual field restrictions to less than 20° in diameter are equally considered blind regardless of visual acuity. However, many countries may have legal definitions which are distinctly different from these, such as Germany, where definitions tend to be much stricter. Blind according to German regulations is defined as best-corrected visual acuity of 1/50 or less in the better eye or a visual field restriction to no more than the central 5°. Severe visual impairment is defined as a visual acuity of not more than 1/20 in the better eye or a restriction of the visual field to the central 10° (Finger 2007; Finger et al. 2011a, b).

### 3.2.2 Main Causes

All main causes of blindness and visual impairment in the elderly are age-related diseases, that is, their prevalence increases with age. An analysis of pooled data from a number of large, population-based, epidemiological studies has demonstrated

that causative disorders differ between white, black and Hispanic persons (Congdon et al. 2004). As most of this data originates from studies conducted in the USA, it is unclear as to how the main causes of blindness and visual impairment differ in other countries. However, it is to be expected that a similar pattern is observed to some extent. The main causes of blindness and visual impairment by race are depicted in Fig. 3.1.

The main causes of blindness have changed considerably over the last 30 years. Our analysis of data from the largest blind register in Germany demonstrates a shift in prevalence from diseases for which treatment or better treatment has become available, such as glaucoma and retinal detachments, to age-related macular degeneration (AMD). We found a slight increase in the number of persons registered blind due to diabetic eye disease and virtually no change in hereditary retinal degenerations such as retinitis pigmentosa over the last 30 years (Table 3.2). The increase in diabetic eye disease leading to blindness is somewhat expected given the general increase in the prevalence in diabetes in all high-income countries.

### 3.2.3 Prevalence Estimates

The *Eye Diseases Prevalence Research Group* has published analyses based on pooled data from eight population-based epidemiological studies. For the USA in the year 2000, it was estimated that there were 937,000 (0.78 %) blind Americans and 2.4 million (1.98 %) Americans with low vision in those aged 40 and older, based on the US definition of blindness and low vision as detailed above (Congdon et al. 2004). These estimates differ by race for the USA, as depicted for causes of low vision in Fig. 3.1. Age-specific blindness prevalence was found to be higher in African American persons compared with white or Hispanic persons, while low vision was more prevalent amongst Hispanic compared to black or white persons (Congdon et al. 2004).

The estimated prevalence published by the WHO for the region of the Americas (North and South America) and based on the WHO definition of blindness and low are: 3.5 blind and 25.6 persons visually impaired per one million population (Pascolini and Mariotti 2012). This amounts to 3.2 million blind and 23.4 million persons with low vision. A direct comparison of these two estimates is impossible due to different underlying definitions, methodologies and reference populations. However, given that the US population above the age of 40 was about 120 million in 2000 (US Census 2000) and the whole population of the region of the Americas is 915 million, it is apparent that blindness as well as visual impairment is very prevalent amongst the elderly population. The large discrepancy in the estimate of persons with low vision is due to the difference in definition, where WHO uses presenting instead of best-corrected visual acuity and a definition of low vision of <6/18 in the better seeing eye. The overall prevalence of blindness and visual impairment steeply increases with age, as shown for the USA in Fig. 3.2.

Applying the prevalence estimates for white persons to Western Europe, blindness for persons older than 40 years in the year 2000 was estimated to be 1.38 million (0.7 %) based on the US definition and 879,000 (0.5 %) based on the WHO definition. Visual impairment was estimated to be 3.64 million (2.0 %; <20/40 in the better seeing eye) (Congdon et al. 2004). The according estimates published by the WHO are 3 blind and 28.7 persons with low vision per million population for the whole of the European region, including all of Eastern Europe (Pascolini and Mariotti 2012). This would amount to a total of 2.7 million blind and 25.5 million visually impaired persons, based on the WHO definition and the total – not only the elderly – population of Europe. Direct comparisons between these estimates are impossible (see above), but they seem to indicate roughly one million blind and three to ten million elderly persons with low vision in Western Europe.

When applying these estimates to the Australian population older than 40 years in the year 2000, current estimates of blindness and visual impairment are: 55,000 (0.7 %) based on the US definition (see above) and 35,000 (0.4 %) based on the WHO definition (see above)

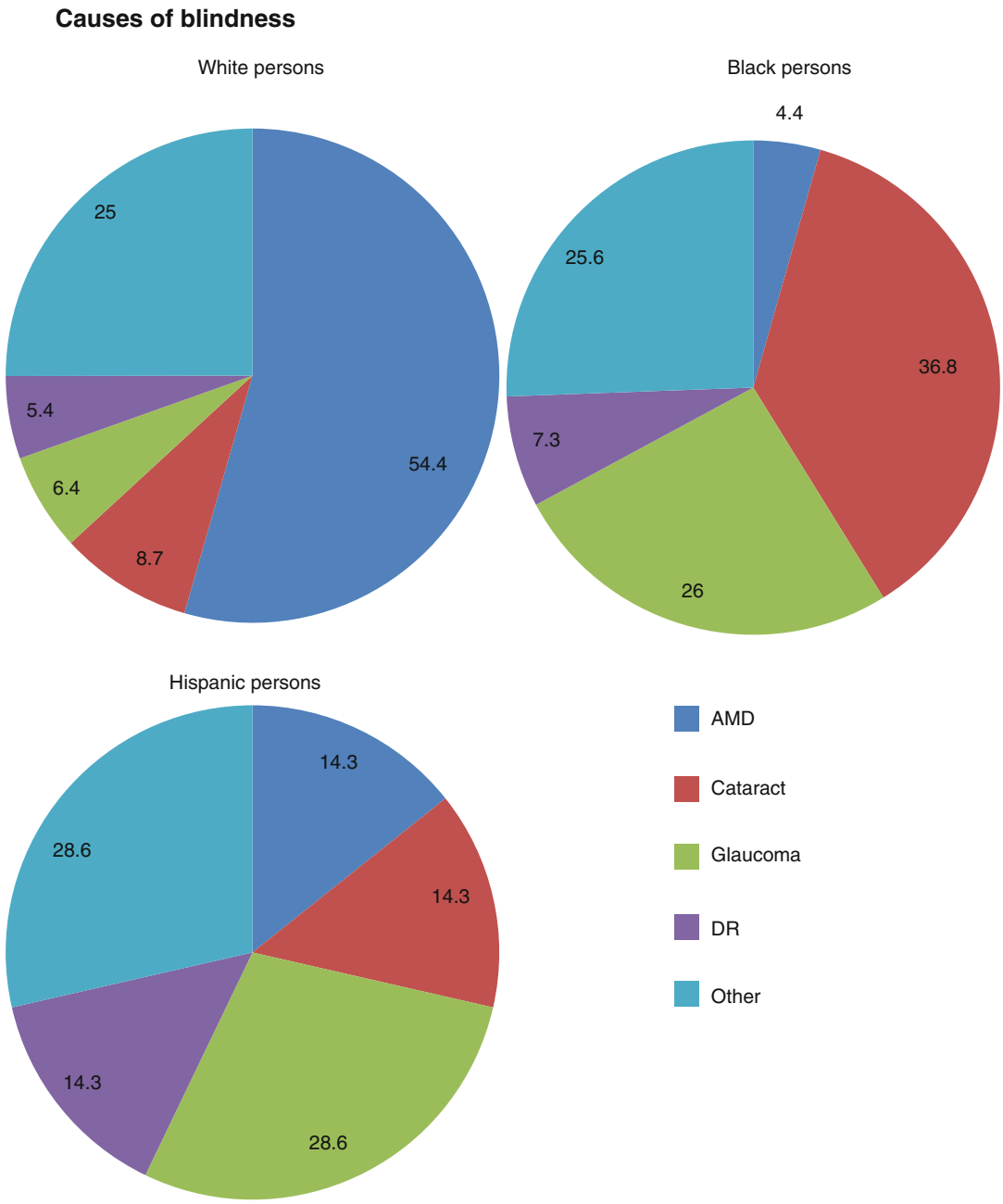


**Fig. 3.1** Causes of blindness[a] and visual impairment[b] by race/ethnicity as defined by the 2000 US Census (Congdon et al. 2004). *AMD* age-related macular degeneration, *DR* diabetic retinopathy. [a]Best-corrected visual acuity <6/60 [20/200] in the better seeing eye. [b]Best-corrected visual acuity <6/12 [<20/40] in the better seeing eye, excluding those classified as blind

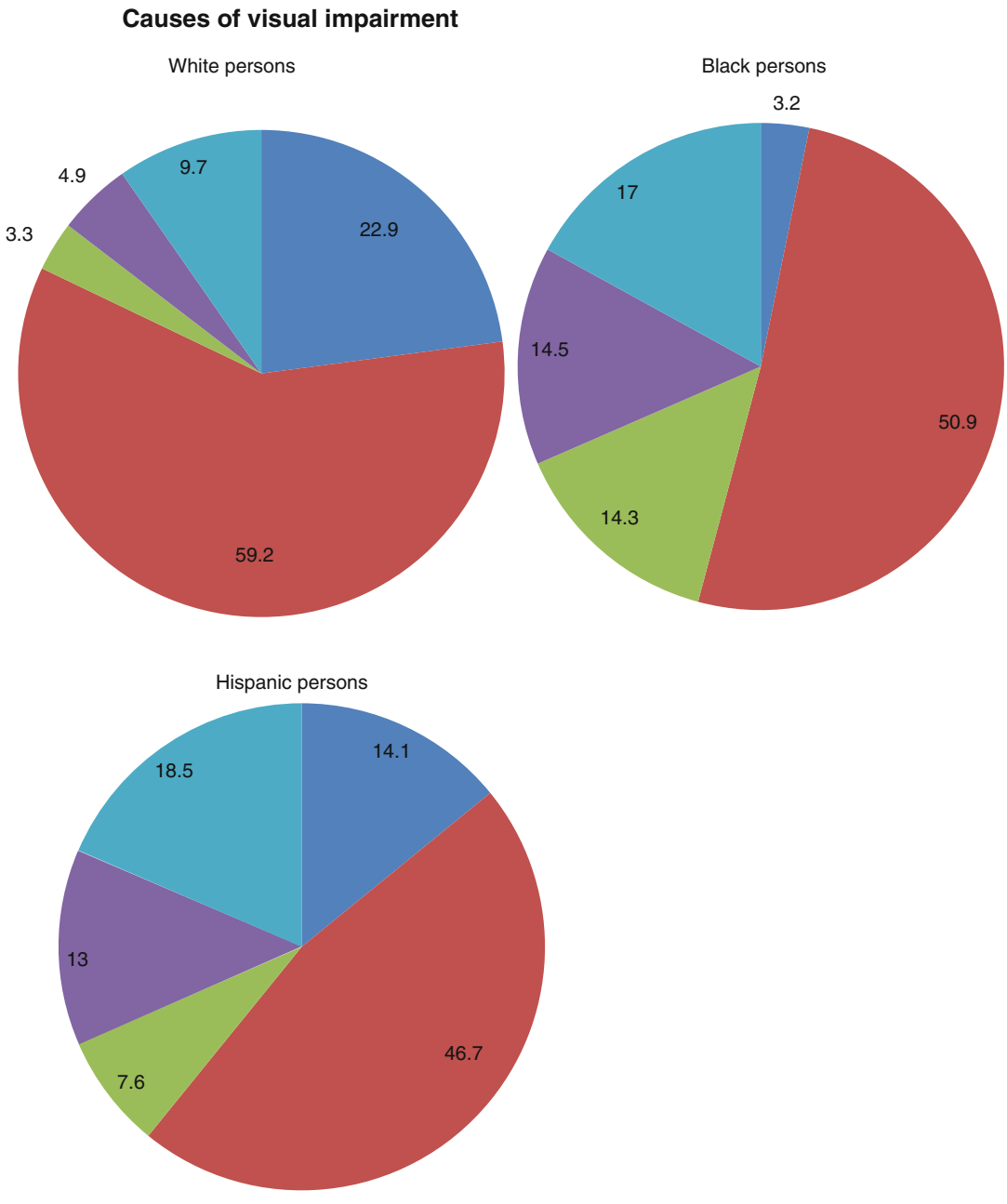


**Fig. 3.1** (continued)

**Table 3.2** Change of main causes of blind registration in Northrhine, Germany, 1978–2006

| Causes | 1978 | 1987 | 1997 | 2006 |
|---|---|---|---|---|
| Age-related macular degeneration | 20.3 | 26.8 | 32.5 | 40.7 |
| Glaucoma and optic atrophy | 24.6 | 21.0 | 20.1 | 15.4 |
| Diabetic eye disease | 6.9 | 8.1 | 8.9 | 9.7 |
| High myopia/retinal detachment | 15.9 | 13.4 | 10.2 | 5.3 |
| Retinitis pigmentosa/ hereditary eye disease | 7.8 | 8.2 | 7.6 | 7.0 |
| Other causes | 24.5 | 22.5 | 20.7 | 19.5 |

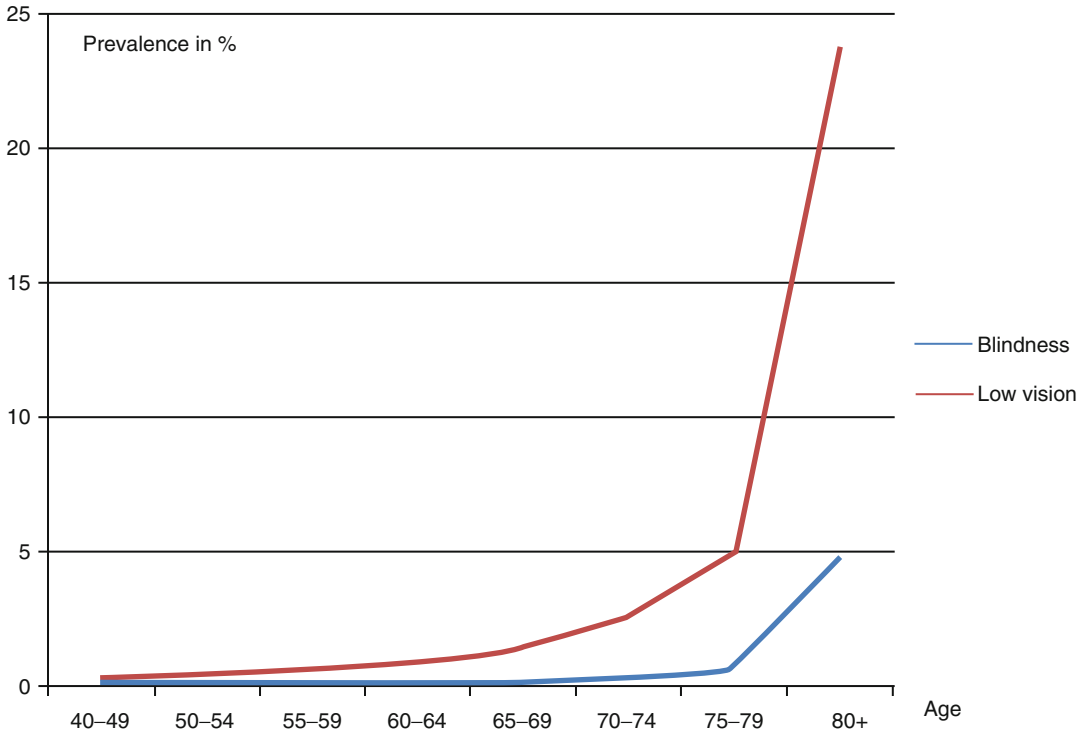


**Fig. 3.2** Prevalence of blindness (using the WHO standard) and low vision by age for the US population, including white, black and Hispanic persons, based on estimates derived from several population-based studies and the 2000 US population (Congdon et al. 2004)

(Congdon et al. 2004). As Australia constitutes only a small percentage of the Western Pacific Region, no separate estimates are available for Australia based on WHO estimates.

### 3.2.4 Incidence Estimates

Several population-based studies have reported the incidence of 5-, 10- and 15-year change in visual acuity leading to mono- or binocular visual impairment and blindness. The BMES, for example, found that, of all eyes under observation for 5 years, 5.1 % developed visual impairment (<20/40), with binocular impairment occurring in 1.7 % (Foran et al. 2003). Women were more often affected than men, although this was no longer statistically significant after adjusting for age. Cataract was the main cause of incident visual impairment at 5 years. Severe visual

impairment (<20/200) occurred in 1.1 % of eyes, of which the vast majority was monocular (Foran et al. 2003). Only 2 out of 2,335 persons followed up at 5 years had developed binocular severe visual impairment, both of whom were women. The main cause for incident severe visual impairment was AMD (Foran et al. 2003). Compared to the BMES, the BDES found a similar incidence of any visual impairment (moderate and severe; <20/40) at 5 years (7.9 % versus 7.1 %) (Klein et al. 1996). Reported incidence rates between studies as well as for the same studies may vary slightly between publications as slightly different definitions of blindness and visual impairment are employed.

The BDES had reported incidence of any visual impairment (≤20/40) and any severe visual impairment (≤20/200) at 10- and 15-year follow-up. At 10-year follow-up, incidence of any visual impairment was 5.9 % and of severe visual impairment 0.8 %, with age (over the age of 75 at baseline) being the most important risk factor. Residing in a nursing or group home was another independent risk factor for incident visual impairment at follow-up (Klein et al. 2001). At 15-year follow-up, these figures were similar, with slightly more persons having developed incident visual impairment (8 %) and severe visual impairment (0.8 %) for the overall sample. However, the cumulative incidence of visual impairment in persons aged 75 or older was 25 % for visual impairment and 4 % for severe visual impairment, indicating that a decrease of visual acuity in elderly persons is a common finding, in particular in those admitted to a nursing or group home (Klein et al. 2006). The main causes for severe visual impairment were AMD (52 %), followed by central or branch retinal vein occlusion (12 %) and cataract (12 %) (Klein et al. 2006).

Based on our analyses of blind registrations at Germany's largest blind register in the state of Northrhine from 2000 to 2008, the overall incidence of blindness was 11.098/100,000 person-years (PY) (Finger et al. 2011a). The largest amount of new registrations for blind allowance was due to age-related macular degeneration (AMD; 5.555/100,000 PY), followed by glaucoma (1.551/100,000 PY) and diabetic eye disease (DED; 1.158/100,000 PY). Retinal and macular dystrophies (RD) and high myopia led to similar proportions of incident cases (0.51 and 0.44/100,000 PY). Causes of blindness and severe visual impairment classified as "others" let to 1.557 incident cases per 100,000 PY. The most frequent diagnoses summarized into "others" were in descending order: cerebral disease, malformations and colobomas, retinopathy of prematurity (ROP) and uveitis. Stratified by age, the highest number of incident cases was observed to be due to AMD in those aged 80 and over (81.258/100,000 PY), followed by glaucoma in the same age group (14.444/100,000 PY), AMD in those aged 60–79 years (9.565/100,000 PY) followed by diabetic eye disease in this age group (3.651/100,000 PY). Stratified by gender, a larger number of incident cases were female for all causes except for retinal and macular dystrophies (RD). The difference was most marked for AMD and DED in those aged 60–79 years and ≥80 years.

### 3.2.5 Risk Factors for Visual Impairment and Blindness in the Elderly

In order for a risk factor to be established for a particular disease, a causal link has to be generated in a longitudinal study with the future occurrence of the disease of interest. Thus, we disregard all associations reported in cross-sectional studies in this brief paragraph. A more in-depth discussion of risk factors for eye diseases associated with ageing can be found in the chapter by de Jong et al. Risk factors vary by disease, and only risk factors for visual impairment irrespective of underlying disease will be briefly discussed here. Several longitudinal studies have established a number of risk factors for visual impairment, of which the most important is ageing (Foran et al. 2003; Klein et al. 1996; Yonekawa et al. 2011; Dimitrov et al. 2003). Several studies have not found gender to be a risk factor (Dimitrov et al. 2003), except the BDES which reported male gender to

be a risk factor for visual impairment (Klein et al. 1996), and the BMES has reported female gender to be a risk factor for uniocular visual impairment (Foran et al. 2003). History of any ocular disease at the time of examination and presence of diabetes mellitus have also been reported as independent risk factors for future visual impairment, in particular in the US Hispanic population (Yonekawa et al. 2011). Economic factors such as lower socioeconomic status and unemployment have less frequently been reported as independent risk factors (Yonekawa et al. 2011). Likewise, institutionalization as an independent risk factor for visual impairment amongst the elderly has only been reported by the BDES (Klein et al. 1996). The Salisbury Eye Evaluation Study (SEES) has found black participants to be more likely to have visual impairment compared to white and Hispanic participants (Rubin et al. 1997).

Several longitudinal studies have found an association between visual impairment and cognitive function in the general population (Anstey et al. 2001; Lin et al. 2004). These findings are corroborated by evidence from another study which also found near visual impairment (but not distance visual impairment) to be a strong independent predictor of future decline in cognitive function in elderly, community-dwelling persons (Reyes-Ortiz et al. 2005). It is nearly impossible to assess which way this interaction goes, but visual and cognitive impairment are highly correlated in elderly populations. These associations are explored in more detail in the chapter by Rovner et al.

## 3.3 Future Trends in Visual Impairment and Blindness

Generally, visual impairment and blindness in the elderly is largely expected to increase based on current demographic trends in all high-income countries. Projections of blindness and severe visual impairment for Germany (Finger et al. 2011a; Knauer and Pfeiffer 2006) as well as other western countries such as Australia (Foran et al. 2000) show a steep increase until 2030, with a widening gap between men and women which increases with age.

Based on the blind registrations 2000–2008 and future demographic trends, we have forecasted an increase in the incidence of blindness and severe visual impairment of about 25 %, from 10,000 newly registered blind in 2010 to 12,500 in 2030 for Germany (Finger et al. 2011a). In 2030, the female population will exceed the male population by about four million in Germany, of whom more than two million will be ≥80 years. Amongst those, the incidence rates of AMD and DED will be more than four times higher in females compared to males, and incidence rates of glaucoma will be more than two times higher in females. In total, in 2030, the incidence of severe visual impairment and blindness will be more than twice as high in women than for men, which is an increase of about 32 % in the incidence of blindness in women compared to 2010, whereas the incidence in men is expected to increase much less over the next 20 years (by 20 %) (Finger et al. 2011a).

Projections for Australia show a fourfold risk of severe visual impairment for women aged 50 and older compared to men (Foran et al. 2000). Projections for vision-threatening diabetic retinopathy for the United States for 2050 predict a threefold increase, mostly in persons aged 65 and older (Saaddine et al. 2008). Based on our data, the incidence of blinding diabetic eye disease is expected to increase by 20 % until 2030. The increase will be mostly in those aged 60–79 years.

The advent of anti-VEGF therapy for an increasing number of potentially blinding diseases such as neovascular AMD, venous retinal occlusions and diabetic macular oedema will certainly impact the magnitude of incident visual impairment and blindness over the coming decades. It has been estimated that ranibizumab treatment for newly diagnosed neovascular AMD could lead to a reduction

of up to 72 % of incident legal blindness associated with neovascular AMD among non-Hispanic whites in the USA (Bressler et al. 2011). However, other estimates based on UK data have demonstrated the anticipated strong demographic ageing effect to outweigh the beneficial effects of anti-VEGF therapy by 2020 (Minassian et al. 2011). Cases with sight loss due to neovascular AMD are projected to increase from 145,697 in 2010 to 189,890 in 2020 despite available anti-VEGF therapy (Minassian et al. 2011).

However, a number of factors besides demographic ageing play a considerable role in determining trends in incident visual impairment and blindness. Indicative of this is the shift of main causes of blindness reported for Germany's largest blind register from 1978 till 2006 earlier, where new therapies and an improved access to and provision of services as well as better health of the population may have led to less visual impairment. Globally, a trend towards a reduction of visual impairment in particular in older age groups has been reported, due to increased socioeconomic development as well as direct investments of governments into prevention and treatment of visual impairment, in particular in low- and middle-income countries (Pascolini and Mariotti 2012). Posterior segment disease, which is the most common cause for visual impairment and blindness in high-income countries, is becoming increasingly important globally as a major cause of visual impairment, with the current estimates for the proportions of visual impairment caused by age-related macular degeneration, glaucoma and diabetic retinopathy exceeding infective causes such as trachoma and corneal opacities (Pascolini and Mariotti 2012).

In high-income countries, however, available data points towards a possible reduction in the number of new cases of AMD. A reduction of the prevalence of age-related macular degeneration, based on the National Health and Nutrition Examination Survey, from 9.4 (1998–1994 survey) to 6.5 % (2005–2008 survey) has recently been reported for the USA (Klein et al. 2011). Furthermore, new data from the 2003 to 2005 BDES demonstrated a lower incidence of early AMD in more recent birth cohorts, suggesting a birth cohort effect which peaked and is now in decline (Huang et al. 2003; Klein et al. 2008).

Our own data from Germany based on blind registrations from 1997 to 2006 and national disability statistics from 1987 to 2005 for a defined geographical region (Northrhine) indicate an initial increase in the number of blind persons until 1998, with a subsequent stabilization despite the increasingly ageing population. The prevalence of blindness in Northrhine increased from 1978 to 1997 (115–165.6/100,000) before it stabilized in 2006 (163.1/100,000). This trend was reflected by the SBS data for blindness and visual impairment (392–372, per 100,000 in 1987 and 2005, respectively). Standardized prevalence rates for Germany showed a continuous, slight reduction for blindness and visual impairment from 1987 to 2006 regardless of which reference population (German population of 1987, 2010, 2030) was chosen in order to eliminate ageing effects over time. Thus, it emphasizes a slight trend towards a stabilization of the number of blind and severely visually impaired persons in Germany (Fig. 3.3). This may be due to improvements in ophthalmic as well as general healthcare and improved health status of the population. However, the reasons for this observed slight decrease remain elusive, and only large, population-based prospective studies will shed light on this.

## 3.4 Summary

An estimated 2.32 million blind and 6.18 million visually impaired older and elderly persons (older than 40 years) live in high-income countries, based on the population figures in 2000 and the definition of blindness of ≤20/200 and visual impairment ≤20/40 best-corrected visual acuity in the better seeing eye. Main causes of blindness and visual impairment vary by country and race. For white persons, blindness is mostly caused by

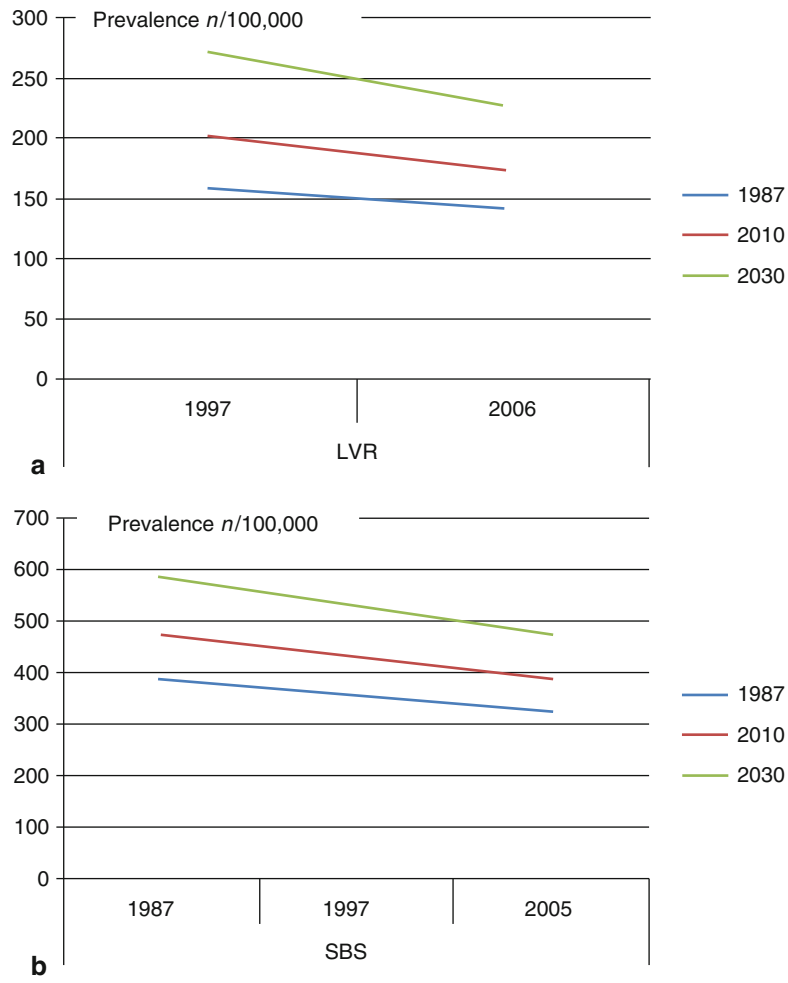


**Fig. 3.3** Standardized prevalence of visual loss. (**a**) Prevalence of blindness (Data from the LVR blind register 1997 and 2006) (**b**) Prevalence of blindness and visual impairment (disability statistics (*SBS*) 1987, 1997 and 2005) using the German population 1987, 2010 and 2030 shows that the prevalence of blindness as well as low vision is decreasing slightly since the late 1980s in Germany

AMD, followed by glaucoma and diabetic eye disease. In black persons, blindness is mainly caused by cataract and glaucoma. In Hispanic persons, the main causes are glaucoma, and to a lesser extent, AMD, cataract and diabetic eye disease. Visual impairment is mostly caused by cataract irrespective of race. Current projections estimate between 5 and 25 % of an elderly population will develop visual impairment and 1–4 % severe visual impairment or blindness over a 5–15-year period, with age being the most significant risk factor. Based on demographic trends, a considerable increase in the number of visually impaired and blind elderly is to be expected. However, recent studies have shown a decreasing prevalence of AMD in the USA as well as a stabilization of new cases of registered blindness in Germany which give rise to the hope that – despite the ever ageing populations – the amount of incident blindness and visual impairment will remain at its current level. This would mean that we have a realistic chance to address and alleviate this considerable burden by research efforts and appropriate service provision in the future.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Anstey KJ, Luszcz MA, Sanchez L (2001) Two-year decline in vision but not hearing is associated with memory decline in very old adults in a population-based sample. Gerontology 47(5):289–293

Bressler NM, Doan QV, Varma R, Lee PP, Suner IJ, Dolan C et al (2011) Estimated cases of legal blindness and

visual impairment avoided using ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. Arch Ophthalmol 129(6):709–717

Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS et al (2004) Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 122(4):477–485

Dimitrov PN, Mukesh BN, McCarty CA, Taylor HR (2003) Five-year incidence of bilateral cause-specific visual impairment in the Melbourne Visual Impairment Project. Invest Ophthalmol Vis Sci 44(12):5075–5081

Finger RP (2007) Blindheit in Deutschland: Dimensionen und Perspektiven (Blindness in Germany: dimensions and perspectives). Ophthalmologe 104(10):839–844

Finger RP, Fimmers R, Holz FG, Scholl HP (2011a) Incidence of blindness and severe visual impairment in Germany – projections for 2030. Invest Ophthalmol Vis Sci 52:4381–4389

Finger RP, Fimmers R, Holz FG, Scholl HP (2011b) Prevalence and causes of registered blindness in the largest federal state of Germany. Br J Ophthalmol 95: 1061–1067

Foran S, Wang JJ, Rochtchina E, Mitchell P (2000) Projected number of Australians with visual impairment in 2000 and 2030. Clin Experiment Ophthalmol 28(3):143–145

Foran S, Mitchell P, Wang JJ (2003) Five-year change in visual acuity and incidence of visual impairment: the Blue Mountains Eye Study. Ophthalmology 110(1): 41–50

Huang GH, Klein R, Klein BE, Tomany SC (2003) Birth cohort effect on prevalence of age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 157(8):721–729

Klein R, Klein BE, Lee KE (1996) Changes in visual acuity in a population. The Beaver Dam Eye Study. Ophthalmology 103(8):1169–1178

Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ (2001) Changes in visual acuity in a population over a 10-year period: the Beaver Dam Eye Study. Ophthalmology 108(10):1757–1766

Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE (2006) Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. Am J Ophthalmol 142(4):539–549

Klein R, Knudtson MD, Lee KE, Gangnon RE, Klein BE (2008) Age-period-cohort effect on the incidence of age-related macular degeneration: the Beaver Dam Eye Study. Ophthalmology 115(9):1460–1467

Klein R, Chou CF, Klein BE, Zhang X, Meuer SM, Saaddine JB (2011) Prevalence of age-related macular degeneration in the US population. Arch Ophthalmol 129(1):75–80

Knauer C, Pfeiffer N (2006) Erblindung in Deutschland – heute und 2030 (Blindness in Germany – today and in 2030). Ophthalmologe 103(9):735–741

Lin MY, Gutierrez PR, Stone KL, Yaffe K, Ensrud KE, Fink HA et al (2004) Vision impairment and combined vision and hearing impairment predict cognitive and functional decline in older women. J Am Geriatr Soc 52(12):1996–2002

Minassian DC, Reidy A, Lightstone A, Desai P (2011) Modelling the prevalence of age-related macular degeneration (2010–2020) in the UK: expected impact of anti-vascular endothelial growth factor (VEGF) therapy. Br J Ophthalmol 95(10):1433–1436

Pascolini D, Mariotti SP (2012) Global estimates of visual impairment: 2010. Br J Ophthalmol 96:614–618

Porz G, Scholl HP, Holz FG, Finger RP (2010) Methoden zur Ermittlung personlicher Krankheitskosten am Beispiel retinaler Erkrankungen (Methods for estimating personal costs of disease using retinal diseases as an example). Ophthalmologe 107(3): 216–220, 22

Reyes-Ortiz CA, Kuo YF, DiNuzzo AR, Ray LA, Raji MA, Markides KS (2005) Near vision impairment predicts cognitive decline: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly. J Am Geriatr Soc 53(4):681–686

Rubin GS, West SK, Munoz B, Bandeen-Roche K, Zeger S, Schein O et al (1997) A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci 38(3): 557–568

Saaddine JB, Honeycutt AA, Narayan KM, Zhang X, Klein R, Boyle JP (2008) Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: United States, 2005–2050. Arch Ophthalmol 126(12):1740–1747

Taylor HR, Pezzullo ML, Keeffe JE (2006) The economic impact and cost of visual impairment in Australia. Br J Ophthalmol 90(3):272–275

West S, Sommer A (2001) Prevention of blindness and priorities for the future. Bull World Health Organ 79(3):244–248

World Health Organization (1990) International classification of diseases, 10th revision. World Health Organization, Geneva

Yonekawa Y, Varma R, Choudhury F, Torres M, Azen SP (2011) Risk factors for four-year incident visual impairment and blindness: the Los Angeles Latino Eye Study. Ophthalmology 118(9):1790–1797

# Part II

# Risk Factors, Genetics, Gene-Environment Interactions and Prophylaxis

# Cataract, Age-Related Macular Degeneration, and Primary Open-Angle Glaucoma: Risk Factors

4

Paulus T.V.M. de Jong

## Abbreviations

| | |
|---|---|
| AMD | Aging macula disorder age-related macular degeneration, all types |
| AREDS | Age-related eye disease study |
| AV | Arteriovenous |
| AVR | Arteriovenous ratio |
| BP | Blood pressure |
| CaV | Cardiovascular |
| CaVD | Cardiovascular disease |
| CDR | Cup-to-disc ratio |
| CeVD | Cerebrovascular disease |
| CI | 95 % confidence interval |
| CHD | Coronary heart disease |
| dAMD | Dry late AMD similar as geographic atrophy |
| eAMD | Early AMD |
| GON | Glaucomatous optic neuropathy |
| GVFL | Glaucomatous visual field loss |
| HR | Hazard ratio |
| HT | Hypertensive |
| htOAG | Hypertensive OAG |
| IOP | Intraocular pressure |
| lAMD | Late AMD includes dAMD and wAMD |
| NT | Normotensive |
| ntOAG | Normotensive OAG |
| OAG | Open-angle glaucoma |
| OHT | Ocular hypertension |
| OR | Odds ratio |
| PeP | Perfusion pressure |
| POAG | Primary open-angle glaucoma |
| PSC | Posterior subcapsular cataract |
| PuP | Pulse pressure |
| RCT | Randomized clinical trial |
| RR | Relative risk |
| VCDR | Vertical cup-to-disc ratio |
| VF | Visual field |
| VFL | Visual field loss |
| wAMD | Wet (neovascular) late AMD |

P.T.V.M. de Jong, MD, PhD, FARVO, FEBOphth, FRCOphth
NIN, Meibergdreef 47,
1105BA, Amsterdam,
The Netherlands

AMC, Department of Ophthalmology,
Meibergdreef 9, 1105BA, Amsterdam,
The Netherlands

LUMC, Department of Ophthalmology,
Albinusdreef 2, 2300RC Leiden,
The Netherlands
e-mail: p.dejong@nin.knaw.nl

## 4.1 Introduction

"Risk" factors as mentioned in the title should refer to factors that have been found to increase the probability of acquiring a disorder. Risk factors do not automatically imply causality which can be demonstrated by aging: it is a risk factor for the three disorders in the title, but it is not the cause of these disorders. Causality can be assumed by the weight of evidence from a number of studies including strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, analogy, and experimental evidence (Hill 1965), but causality is never definite. "Even the most

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_4, © Springer-Verlag Berlin Heidelberg 2013

careful and detailed mechanistic dissection of individual events cannot provide more than associations, albeit at a finer level" (Rothmann 1998). One epidemiological design to establish causality is a clinical trial in which we rely on randomization to balance treated or exposed groups and non-treated or non-exposed groups. A clinical trial, however, may have more problems obtaining well-balanced controls, and in case of diseased persons, its results are not necessarily applicable to the general population. In general, control persons in clinical trials will be healthier than the normal population and that also may make their results less generalizable to the target population. This holds also for case control studies that tend to compare the very ill with the very healthy ones. Prospective studies that follow groups with specific risk factors for incidence of disease can also be powerful because of the temporality. However, population-based studies which follow groups over time may suffer from loss to follow-up or a lack of power when the disease of interest is relatively rare, but their advantage above clinic-based case–control studies is that the selection of controls from a population is often less biased. Also it should be kept in mind that access to clinical care may vary widely worldwide and that clinic-based study results may not be applicable to other populations. In one recent population-based study from the USA, for example, about 60 % of the participants had no health insurance (Choudhury et al. 2011). Even within a Canadian clinic, poorer patients declined more expensive treatment (Chew et al. 2005).

There are an increasing number of tools to test the validity of conclusions in medical articles. In treatment efficacy and safety, one considers a meta-analysis of multiple, validly performed, randomized clinical trials (RCTs) as one of the highest levels of evidence, but these criteria are not always applicable to observational studies, as shown below. Risk factors are often derived from observational studies, and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) group made a checklist of 22 items used in case–control, cross-sectional, and cohort studies (Vandenbroucke et al. 2007). Among these 22 items are, for example, prespecified hypotheses, key elements of study designs, sources of bias, nonparticipation, and loss to follow-up. There is a wide range of risk factors for the disorders to be discussed in this chapter, but there is also a wide variation in the level of evidence for such factors. Without claiming completeness, Table 4.1 provides the reader with an idea of the strength of evidence of risk factors.

Cataracts, primary open-angle glaucoma (POAG) and, less frequently, ageing macula disorder (AMD) are categorized into primary and secondary forms. "Primary" often implies that we do not know the cause, and one could argue that once a cause is established, the disorder is not "primary" anymore. This is not absolute, because we know, for example, that aging or diabetes mellitus are associated with cataracts without knowing their exact pathophysiological mechanisms.

Around 1970, authors rightly decided to get rid of the term "senile" for aging cataract and macular degeneration, but instead of "aging," implying older age, they used the term "age-related" that can also be congenital or juvenile (Straub 1969; Sunness et al. 1985). For that and other reasons (de Jong 2011), I prefer "aging cataract" and "aging macula disorder" (AMD) over "senile" or "age-related cataract" and "age-related macular degeneration," the latter being one and the same as aging macula disorder and therefore has exactly the same acronym: AMD. Cataract and macula disorder in the elderly would be better but would create completely new acronyms and I had to bow for the editors. The reader will see that all three disorders AMD, cataract, and POAG suffer from a lack of international classification or even standardization of definitions, thus hampering comparisons.

## 4.2 Risk Factors for Cataract

Our classic handbooks on this subject (Duke-Elder 1964; Tasman and Jaeger 1999) list around 500 items in the section on cataracts describing nearly 75 different morphological types and around 200 different causes of cataracts. These were collected from publications by often astute and meticulous researchers, sometimes in extreme circumstances like world wars. Many of these past articles probably

**Table 4.1** Quality of risk factor studies and according levels of evidence or conclusions

| Based on | Level of evidence |
|---|---|
| Systematic review/meta-analysis of at least two studies meeting criteria a to k | I |
| Prospective cohort study with<br>(a) Sufficient sample size<br>(b) In a representative population<br>(c) Clear definition of inclusion/exclusion criteria or cases/controls<br>(d) Clearly defined primary outcomes<br>(e) Clearly given comparison of baseline characteristics between groups<br>(f) Adequate control for confounding<br>(g) No selective follow-up<br>(h) Sufficient follow-up time, related to natural history of disorder under study<br>(i) Adequate accounting for loss to follow-up with numbers sufficiently limited to have minimal potential for bias<br>(j) Masked outcome assessment<br>(k) Adequate statistics | I When based on several independent studies with consistent results<br>II When based on only one study |
| Study lacking two or more criteria a to k OR retrospective cohort study OR case–control study meeting criteria a to k, where appropriate | II When based on two studies<br>III When based on one |
| Studies with no control group, OR case reports, OR expert opinions not clearly based on I or II | III |

would show defects according to the STROBE criteria and therefore should be classified as level III evidence, but that does not always deprive them of their value. For instance, how can we prove nowadays with consent from the ethics committee that lightning or electrocution causes cataract (Duke-Elder 1964)? These handbooks draw attention to differences in epidemiological and ophthalmological thinking. It will be nearly impossible in a large population-based cohort study to exclude 200 different causes of cataract in each participant. Thus they might all be classified as aging cataracts, losing quite some specific information on etiology. Another epidemiological hurdle is that there is essentially no universal definition of cataract. Nearly every newborn baby has some lens opacity with an embryological, a fetal and, sometimes, the beginning of an infantile nucleus, and so has cataracts according to the Framingham Eye Study definition: "A cataract is any opacity in the crystalline lens of the eye" (Leibowitz et al. 1980). Epidemiologically this may be correct, but precisely at which point an opacity becomes a clinical cataract is uncertain. Even more so when cataract surgeons become more and more eager to find indications for surgery. Thus risk factors for cataract surgery as an endpoint of cataract seem tricky to study (Chang et al. 2011) when these indications are not specifically mentioned as is the case in most publications. Clinically, cataract may be defined as a lens opacity or clouding that, after exclusion of other causes for visual loss, hampers the patient's visual function in such a way that it hinders her or him from performing desired tasks. It may be clear that this is quite a subjective criterion. The patient should be the one, after hearing the pros and cons of surgery, to decide if the moment has come for an intervention. This clinical definition, however, is hard to apply to the epidemiological search for risk factors. Thus the 75 morphological types of cataract are reduced to a small number, according to different grading systems (Leibowitz et al. 1980; Sparrow et al. 1986; West and Taylor 1986; Chylack et al. 1988; Hockwin 1994; Chew et al. 2010). Frequently, this simplification leads to a division in nuclear, posterior subcortical (PSC), cortical, or mixed cataracts, with each two to five grades per subdivision. It will be clear that this simplification, though necessary when comparing thousands of eyes, discards valuable information. These different grading systems in various studies are another source of confusion in assessing risk factors and might account for the often contradictory results.

**Table 4.2** Examples of secondary or complicated cataract

| Cause | Examples | Subgroups/examples |
|---|---|---|
| Inflammation | Uveitis | Juvenile rheumatoid arthritis |
| | Bacterial/viral infection | Herpes zoster |
| | Following angle-closure glaucoma | "Glaukomflecken" |
| Metabolic disturbances | Anorexia nervosa | |
| | Diabetes mellitus | |
| | Galactosemia | |
| Multiorgan/system syndromes | Alport syndrome | |
| | Mongolism | |
| | Myotonic dystrophy | |
| | Raynaud's disease | |
| | Refsum syndrome | |
| Trauma | | |
| Chemical | Acid or lye burns | |
| | Medicine use | Corticosteroids |
| | Cobalt, gold, mercury, silver | |
| Physical | Perforation of eye | |
| | Contusion of eye | |
| | Irradiation | Ionizing |
| | | UV |
| | | Infrared |
| | Electroshock; lightning | |

As mentioned, cataracts will be divided into primary and secondary cataracts, the latter often clinically termed as "complicated cataract." Once we find a risk factor for cataract, for example, diabetes mellitus or smoking, the exact cause of the cataract may still elude us, and so risk factors and causes may in this context be two different items.

Examples of the easier to define secondary cataracts are cataracts due to chemical or physical trauma, multiorgan syndromes, inflammation, or metabolic disturbances (Table 4.2). However, the majority of those will not be discussed in detail in this chapter. This paragraph on risk factors will be confined to primary cataract (of unknown origin) in persons or populations over the age of 40 years.

## 4.2.1 Risk Factors: Evidence Level I

### 4.2.1.1 Age

We have known for millennia that age is a risk factor. Nevertheless, many papers still mention this nowadays (Leibowitz et al. 1980; Hodge et al. 1995; Chang et al. 2011; Waudby et al. 2011). The prevalence of cataract is 2.35 % between age 40 and 49 years and 74 % over age 80 (Congdon et al. 2004) in white populations. In India, the prevalence of any cataract rose from about 50 % below age 65 to 90 % above age 70 (Vashist et al. 2011).

## 4.2.2 Risk Factors: Evidence Level II

### 4.2.2.1 Gender

In seven studies including black, Hispanic, and white populations, the prevalence of cataracts in females varied between 53.3 and 61.1 % and in males between 38.9 and 46.7 % (Congdon et al. 2004). Also in India and Asia, women had a higher prevalence (Vashist et al. 2011). So, roughly estimated the prevalence of cataracts is 15 % higher in women than in men (West and Valmadrid 1995).

#### 4.2.2.2 Geography

Most studies agree that the prevalence of cataracts is higher in tropical areas with lower latitudes and in higher altitudes (Hollows and Moran 1981; Leske and Sperduto 1983; Brilliant et al. 1983; Javitt and Taylor 1994; Sasaki and Kojima 1994; West and Valmadrid 1995; Sapkota et al. 2010). These differences, however, can also be due to genetics, hygiene, UV radiation at different latitudes, nutrition, toxic factors like cooking fuel, and many more factors. Around age 60, the prevalence of cataract in India is higher than in white populations, but around age 80 these prevalences are similar (Vashist et al. 2011).

#### 4.2.2.3 Light Exposure (Elevated)

It is clear that there may be quite some overlap between this risk factor and the geographical one (see also remarks on light exposure in the AMD section). Nevertheless, in addition to the articles mentioned in the geography paragraph, there seems to be sufficient evidence to consider ultraviolet A and especially B as risk factors (Taylor et al. 1992; Hodge et al. 1995; Italian-American Cataract Study Group 1991; West et al. 1998). Galactic cosmic space radiation could increase cortical cataracts (Chylack et al. 2009). In Reykjavik, Scheimpflug images were taken, and light exposure was not a risk factor for nuclear cataracts (Arnarsson et al. 2002).

#### 4.2.2.4 Smoking

Some early studies claiming smoking as a risk factor for cataract (Christen et al. 1992; Hankinson et al. 1992) were based on retrospective self-reported data. There exist, however, cross-sectional or longitudinal studies that point to smoking as a risk factor for nuclear cataract (Flaye et al. 1989; West et al. 1989a; Arnarsson et al. 2002; Tan et al. 2008b), all types of cataract (Krishnaiah et al. 2005b; Wu et al. 2010) or cataract extraction (Krishnaiah et al. 2005b; Lindblad et al. 2005), encompassing various ethnic groups.

### 4.2.3 Risk Factors: Evidence Level III or Lower

#### 4.2.3.1 Alcohol Intake (Elevated)

Clinic-based case–control studies from the UK and the USA mentioned that heavy alcohol ingestion was associated with cataracts, with a suggestion of a J-shaped curve, which means that moderate ingestion might be protective (West and Valmadrid 1995). A population-based prevalence study found similar associations (Ritter et al. 1993) especially for consumption of more than four alcohol units a day (Klein and Klein 2007). Other studies could not corroborate this (Hodge et al. 1995; Wang et al. 2008). Alcohol and smoking often went hand in hand, and one should keep in mind that both are based on history data. The overall picture seems to be that alcohol has a minor influence, if any, on cataract formation (Wang et al. 2008).

#### 4.2.3.2 Antioxidant Levels (Reduced), Nutrients, and Vitamin Supplements

There is disputed evidence as to whether nutrients play a role in the formation of aging cataracts, and if so, which nutrients are the important ones. Often an association with only nuclear sclerosis or PSCs was found, and natural diet and supplements were intermingled in the analyses (Hodge et al. 1995). Multivitamin supplements decreased the prevalence of nuclear cataracts (Sperduto et al. 1993; Chang et al. 2011), and antioxidants seem to reduce the prevalence of cataract (West and Valmadrid 1995; Karppi et al. 2012). In AREDS, it was found in a RCT that antioxidants (vitamins C and E, beta-carotene) had no effects on risk or development of cataracts (Age-Related Eye Disease Study Research Group 2001). In a very detailed review on nutrients and supplements, the evidence for protection against cataracts does not appear to be convincing (Chiu and Taylor 2007), but in an Indian vitamin C-depleted population, there was an inverse association between vitamin C and cataract (Ravindran et al. 2011a). One should

keep in mind that serum vitamin C levels are lower in Indian than in Western populations (Ravindran et al. 2011b).

#### 4.2.3.3 Body Mass Index (BMI) (High)

It is stated that both a low BMI (Athanasiov et al. 2008) especially in malnourished populations and a high BMI is associated with nuclear cataracts (Lim et al. 2009) in Asian populations. Another population-based longitudinal study found an increased risk of cortical cataracts and PSCs in persons with a high BMI (Younan et al. 2003).

#### 4.2.3.4 Cardiovascular Disease

Cataracts were associated with systemic hypertension (Kahn et al. 1977), but the subsequently reviewed literature was inconclusive (West and Valmadrid 1995). A longitudinal study found that hypertensive patients had an odds ratio (OR) of 3.4 for PSCs and more cataract surgery was performed on participants with a history of angina (Younan et al. 2003). Concerns might be raised that there could be confounding by indication through cataract-causing antihypertensive drugs. Also surgeons might be inclined to operate earlier on angina patients before the cardiac risk becomes too high for such a procedure.

#### 4.2.3.5 Educational Status (Low)

Higher education in general is associated with a higher socioeconomic status as well as a healthier lifestyle with regard to food intake, smoking, and access to health services (Kahn et al. 1977; West and Valmadrid 1995; Chang et al. 2011). Most studies find that higher education is associated with less cataract (Xu et al. 2010; Wu et al. 2010).

#### 4.2.3.6 Ethnicity

Aborigines have more cataracts than non-Aborigines (Hollows and Moran 1981). The population-based Barbados study showed a higher incidence of cataracts in blacks than whites (Leske et al. 2004) as did a clinic-based study with only 4 % black participants (Chang et al. 2011). The same difficulties in ascertaining causality in the case of education, geography, light exposure, and nutrition may apply here (West et al. 1998).

#### 4.2.3.7 Genetics

As is common nowadays, aging cataracts are considered to be a multifactorial disease. Contrary to congenital and familial or syndromal cataracts, hardly any of the genes are known. Two recent reviews highlight our present state of knowledge (Sanfilippo et al. 2010; Shiels et al. 2010). In a female twin study on nuclear cataracts, the variance in expression was in 48 % determined by genetics, in 38 % by age, and in 14 % by environment (Hammond et al. 2000). The prevalence of cortical cataracts was similar for monozygotic and dizygotic twins, and although there were marked differences between clinical and digitized gradings, the genetic influence was estimated to be 45 %, the environmental one 30 %, and that of age 14 % (Hammond et al. 2001) although twin studies might overestimate these risks.

#### 4.2.3.8 Hormone Replacement Therapy (HRT)

The literature on HRT and cataracts is controversial. Cross-sectional studies suggested a protective effect, but longitudinal studies did not (Klein et al. 2000; Freeman et al. 2004; Younan et al. 2003; Kanthan et al. 2010). One study mentioned a higher risk for cataract surgery in women using HRT at any time (Lindblad et al. 2005). A main concern for papers with cataract surgery as an outcome is the continuously changing indications for cataract surgery in high-volume cataract clinics. In underdeveloped countries, it may be the other way round – people who need surgery do not get it. Surgery in that situation might depend more on sufficient means for transport, care, and surgery fees.

#### 4.2.3.9 Refraction

For many years, it was the conventional wisdom of clinicians that myopic eyes develop nuclear cataracts at an earlier age than emmetropic or hyperopic eyes. This concept seems too simple. Most eyes undergo a hyperopic shift until the age of 65 or 70 years and after that a myopic shift. This holds true for different ethnicities (Lee et al. 1999; Guzowski et al. 2003; Wu et al. 2005; Fotedar et al. 2008). The more nuclear cataract was present at baseline (around age 40

years), the higher the myopic shift after 5 years (Lee et al. 1999).

## 4.3 Risk Factors for Aging Macula Disorder (AMD)

As with cataracts, there are different classification or grading systems for AMD. Most of them stick to an arbitrary age limit of 40 years or older for the patient or the participant in a study and the obligatory presence of drusen. Drusen are white, well-demarcated dots in the retina and may be small (<63 μm) to large (≥125 μm) in size when seen with a certain standard magnification on fundus color transparencies or digitized images. There is also a tendency to separate AMD into early AMD (eAMD) and late AMD (lAMD). Often eAMD is subdivided in two to three mutually exclusive classes, characterized by increasing numbers and sizes of drusen and the presence of hyperpigmented or hypopigmented spots in the retina or its pigment epithelium (van Leeuwen 2003b). Usually the person with eAMD has no or few visual complaints. Commonly, lAMD is subdivided in a dry form (dAMD), also called geographic atrophy, and a wet (wAMD) or neovascular form. dAMD is considered to be the result of dying retinal pigment epithelial cells with subsequent photoreceptor cell loss, leading to gradual vision loss. On the other hand, wAMD originates from subretinal neovascular membranes with subsequent hemorrhages and scar tissue formation in the center of the retina; it can lead to visual loss in a few weeks or even overnight. In this chapter, the term AMD refers to all types of AMD.

At present, most epidemiological studies exclude certain retinal abnormalities to reach a diagnosis of AMD and do not use visual acuity in an eye as a diagnostic criterion for AMD. We have to keep in mind that AMD is always a diagnosis by exclusion of others, and this may be another misclassification pitfall, especially in retrospective studies, because several different end-stage retinal disorders resemble each other. Table 4.3 provides the most common disorders that may mimic AMD.

### 4.3.1 Risk Factors: Evidence Level I

#### 4.3.1.1 Aging

By definition, age is a risk factor for AMD. The estimated prevalence of drusen ≥125 μm goes from 2.6 % at age 50 years to 27.5 % above age 80 years. For dAMD, this goes from 0.13 to 8 % and for wAMD from 0.18 to 9.5 %. For any lAMD, these figures rise from 0.27 to 13.6 % (Friedman et al. 2004a). A recent meta-analysis on 17,236 lAMD cases confirmed age as a risk factor in all studies (Chakravarthy et al. 2010). The OR for AMD rose with 4.2 (95 % CI 3.8–4.6) per decade (Rudnicka et al. 2012).

#### 4.3.1.2 Cataract Surgery

It remains questionable whether or not cataract surgery elevates the long-term risk of lAMD in patients with no AMD or only eAMD by whatever mechanism, light exposure, or surgical trauma (van der Schaft et al. 1994). Thus perhaps this should be evidence level II. Two publications stated that there was no conclusive evidence and that a RCT was indicated (Smith et al. 2005; Patel 2007). Because no such trials were performed, a recent Cochrane review concluded: "At this time, it is not possible to draw reliable conclusions from the available data to determine whether cataract surgery is beneficial or harmful in people with AMD" (Casparis et al. 2009). Nevertheless, several prospective population-based studies found increased ORs up to 3.8 of late AMD after cataract surgery (Freeman et al. 2003; Krishnaiah et al. 2005a; Cugati et al. 2006; Ho et al. 2008; Fraser-Bell et al. 2010; Choudhury et al. 2011). A large meta-analysis of prospective cohort studies found that cataract surgery is a strong risk factor for wAMD (relative risk (RR) 3.05; 2.05–4.55) (Chakravarthy et al. 2010).

#### 4.3.1.3 Smoking

Smoking is one of the best documented risk factors for AMD (Chakravarthy et al. 2010; Krishnaiah et al. 2005a) since it was first demonstrated in a clinic-based case–control study that smokers developed AMD on average 7 years earlier than nonsmokers (Paetkau et al. 1978). Smoking as a risk factor was found in

**Table 4.3** Examples of retinal disorders mimicking early or late AMD to be excluded before a definition of AMD can be made

| Mimicking | Causes/examples | Subgroups |
|---|---|---|
| Early AMD | Asteroid hyalosis | |
| | Circinate retinopathy | |
| | Diabetic exudates | |
| | Hypertension | |
| | Kidney disorders | |
| | Hyperpigmentations | Medicine induced |
| | | Systemic hypertension |
| | Infections | Disseminated choroiditis, sarcoid, tbc, histoplasmosis |
| | Punctate inner choroidopathy | |
| | Retinitis punctata albescens | |
| | Stargardt disease | |
| | Telangiectasia | |
| Late dry AMD | Areolar macula dystrophy | |
| | Coloboma (congenital) | |
| | Cone dystrophy | |
| | Maternally inherited diabetes and deafness | |
| | Myopia | |
| | Infections | Zoster retinitis, toxoplasmosis |
| | | Toxocara |
| | Trauma | Eclipse retinopathy |
| | | Photo/cryocoagulation/radiation |
| Late wet AMD | Angioid streaks | |
| | Choristoma | |
| | Disciform reaction in any retinal scar | |
| | Haemangioma | |
| | Infection | Presumed histoplasmosis |
| | Metastatic disorders | Breast carcinoma |
| | Trauma; choroidal rupture | |

similar studies in white (Hyman et al. 1983) and Japanese persons (Tamakoshi et al. 1997) and also in twin studies (Seddon et al. 2006). Also in prevalence studies in Australia (McCarty et al. 2001), China (Yang et al. 2011), Europe (Vinding et al. 1992), and India (Krishnaiah et al. 2005a) and in Latinos (Fraser-Bell et al. 2008) and South Asians (Cackett et al. 2008). Finally, it was best documented in population-based cohort studies in Australia (Mitchell et al. 2002b) and Europe (van Leeuwen et al. 2003b) and in white people (Klein et al. 2002) although only for eAMD, and Latinos (Choudhury et al. 2011) in the USA, as well as in pooled data from these studies (Tomany et al. 2004).

### 4.3.2 Risk Factors: Evidence Level II

#### 4.3.2.1 Body Mass Index (BMI) (Elevated)

A recent review concluded that there is considerable evidence for an association between high BMI and AMD. The different associations with various types of AMD remain to be determined (Cheung and Wong 2007). Data from a RCT gave an OR 1.05 (95 % confidence interval (CI) 1.001–1.10) per 1 kg/m$^2$ rise in BMI (Klein et al. 2007a). There is hope for obese people. A decrease in waist-to-hip ratio of 3 % or more resulted, in a population-based cohort followed for 6 years, in lower odds for any AMD. Those losing 3 % waist-to-hip ratio had a 29 % drop in

odds, and the obese ones who were in the bottom decile of waist-to-hip ratio change dropped 59 %. Unfortunately, only 2 % of the obese reached this bottom decile (Peeters et al. 2008).

#### 4.3.2.2 Family History (Positive)

Both in a clinic-based case–control study (Hyman et al. 1983) and a population-based cohort study (Klaver et al. 1998), a positive family history is a risk factor for AMD. More details will be provided in Chap. 5.

#### 4.3.2.3 ω-3 Fatty Acids (Reduced) or Limited (Oily) Fish Ingestion

One of the first studies mentioning an inverse association between fish intake and AMD was based on small numbers (0.6 % of the cohort) and retrospective AMD data with a visual criterion ≤20/30 within the definition of AMD (Cho et al. 2001). A prospective study saw a just significant reduction of lAMD with an OR 0.25 for those who consume fish at least three times a week (Chua et al. 2006). After 10-year follow-up, the same group found that one fish serving per week reduced the risk of eAMD (RR 0.69) in people with below-median linoleic acid consumption (Tan et al. 2009). One concern is that two or more fish servings failed to do so and that intake of nuts showed a similar pattern in that study. Furthermore, lAMD was not mentioned in the 10-year report. In a cross-sectional population-based study, eating oily fish at least once a week halved the risk of wAMD (Augood et al. 2008). Similar protective effects were found in prospective population-based studies in combination with some genotypes (Wang et al. 2009) and various other genetic variants (Ho et al. 2011). A meta-analysis found a reduced risk of lAMD in high dietary intake of ω-3 fatty acids or twice a week fish intake but concluded that there was insufficient evidence to support these as factors in AMD prevention (Chong et al. 2008b).

#### 4.3.2.4 Refraction: Hyperopia

Since clinical case–control (Maltzman et al. 1979; Hyman et al. 1983) and most cross-sectional population-based studies (Kahn et al. 1977; Goldberg et al. 1988; Wang et al. 1998) linked hyperopia with AMD, this was also confirmed for shorter axial length (Lavanya et al. 2010). One population-based study could not confirm this (Klein et al. 1998) nor could its follow-up (Wong et al. 2002). Another longitudinal population-based study could not confirm their cross-sectional finding that hyperopia was a risk factor for eAMD (Wang et al. 2004). Yet another population-based study found that hyperopia was associated with both prevalent and incident AMD; the risk of AMD increased after 5 years per diopter of hyperopia by 5 % (Ikram et al. 2003).

Obviously, there is a huge difference in cross-sectional and follow-up studies, and it is also clear that longitudinal studies do not always seem to provide the final answer. On the one hand, the differences may be explained by power problems. On the other hand, naturally changing refraction since baseline toward hyperopia below age 65 years and myopia above that age (Fotedar et al. 2008; Gudmundsdottir et al. 2005) may be a factor. It seems clear that there is an increasing risk of AMD with increasing hyperopia with crude RRs, going from 0.6 in myopia < −3.00 diopters (D) and 0.3 from −1.00 to −3.00 D, to 2.5 for hyperopia from +1.00 to +2.25 D, and 3.6 for hyperopia over +2.5 D (Wong et al. 2002), although the RRs became nonsignificant after adjusting for age. The difference between this latter study and the one by Ikram may be the statistical analysis: Wong used both eyes of a participant, while Ikram took the eye with the higher level of AMD or, when there was no difference, the right eye.

### 4.3.3 Risk Factors: Evidence Level III or Lower

#### 4.3.3.1 Alcohol Intake (Elevated)

The role of alcohol consumption in AMD is a matter of dispute. Prospective population-based studies found no risk (Boekhoorn et al. 2008) or even a slightly protective effect (Arnarsson et al. 2006), while others found that over four consumptions a day increased the risk of dAMD (Knudtson et al. 2007) or only eAMD (Chong et al. 2008a). In addition, retrospective data from

a randomized trial found no marked risk (Ajani et al. 1999) so that, overall, it seems that alcohol is not a significant risk factor for AMD.

#### 4.3.3.2 Arteriovenous (AV) Caliber of Retinal Vessels, Arteriovenous Ratio (AVR), Focal Narrowing, and AV Nicking

The AV caliber or their ratio was not associated with AMD (Ikram et al. 2005), but AV nicking had an OR 2.6 (95 % CI 1.2–5.5) for late AMD (Liew et al. 2006); this could not be confirmed in another study (Cheung et al. 2011; van Leeuwen et al. 2003a). Finally, one cross-sectional study found an association between wider venular caliber and eAMD (Jeganathan et al. 2008). For the time being, AV caliber or the AVR seem not to be major risk factors.

#### 4.3.3.3 Cardiovascular (CaV-CaVD) and Cerebrovascular Disease (CeVD)

Like the Framingham Eye Study (Kahn et al. 1977), a clinic-based case–control study found that hypertension is a risk factor for eAMD and wAMD as did a population-based cohort study (van Leeuwen et al. 2003a). Among Latinos, the link with wAMD held only for diastolic but not for systolic hypertension; high pulse pressure was a risk factor for AMD (van Leeuwen et al. 2003a; Choudhury et al. 2011), while low pulse pressure protected against wAMD (Fraser-Bell et al. 2008). A clinic-based case–control study found that better CaV health was associated with prevalent AMD (McCarty et al. 2008). Coronary heart disease (CHD) was associated with eAMD but not with lAMD (Sun 2012). Various measures of atherosclerosis were a risk for AMD (van Leeuwen et al. 2003a). In a meta-analysis, no prospective studies could find hypertension, CaVD, or CeVD to be a risk factor for AMD, but some case–control studies did (Chakravarthy et al. 2010). Conversely, cases with AMD had no increased risk of CHD or CaVD (Fernandez et al. 2012). One prospective population-based study differentiated CeVD and found that lAMD was a risk factor for any stroke and especially for cerebral hemorrhage but not for cerebral infarction (Wieberdink et al. 2011). All in all, CaVD nor CeVD seems to be a major risk factor.

#### 4.3.3.4 Cholesterol, High-Density Lipoprotein (Elevated Serum Levels)

A meta-analysis of five prospective and six cross-sectional studies could not find significant ORs or RRs for serum total or HDL cholesterol levels and AMD (Chakravarthy et al. 2010).

#### 4.3.3.5 Diabetes Mellitus

Diabetes is also a difficult risk factor to study because of the many different criteria for its diagnosis. These may vary from the many ways of obtaining historical data on the presence of diabetes to the use of oral treatment or injections and to measuring glucose levels in the blood. The latter may be performed randomly, after fasting overnight or even after a loading test. This having said, diabetes was not a risk factor for AMD in the pooled analysis of three large population-based incidence studies on mostly white participants (Tomany et al. 2004) and in a subsequent analysis of dAMD (Klein et al. 2008). A borderline significance was found in blacks (Leske et al. 2006).

#### 4.3.3.6 Ethnicity

In a cross-sectional population-based study, eAMD and lAMD were more prevalent in whites than blacks (Friedman et al. 1999) like in another such study (Bressler et al. 2008) but for wAMD. Estimated prevalence of wAMD was 16 times and of dAMD 40 times higher in whites than in blacks (Friedman et al. 2004a). However, another population-based study in the USA using a non-mydriatic camera found a lower prevalence of eAMD in blacks but no major differences in prevalence of lAMD between Asians, blacks, Hispanics, or whites (Klein et al. 2006). Only Native American ancestry seemed to predispose to dAMD (Fraser-Bell et al. 2005). Another study on Hispanics in Arizona found a higher prevalence of eAMD but a lower of lAMD than in whites (Munoz et al. 2005). The prevalences of eAMD seemed to be similar in Japan as in

a white Australian population, but lAMD was lower among Japanese women (Kawasaki et al. 2008). The 9-year incidence of lAMD in Japan was lower than among whites and higher than in blacks (Yasuda et al. 2009). The same prevalences were found in a white rural population as in an urban one in Italy (Piermarocchi et al. 2011), and there was a similar prevalence in Spain (SEESG 2011). Rural Chinese had similar prevalences as whites for eAMD, but the prevalence was lower for lAMD (Yang et al. 2011). There were no major differences in prevalence of lAMD between blacks, Chinese Asians, whites, and Hispanics (Chakravarthy et al. 2010) and Indian or Malay populations (Cheung et al. 2012).

#### 4.3.3.7 Gender, Female Hormones, and Hormone Replacement Therapy (HRT)

Presumed lower prevalences of AMD in women led to hypotheses that more years of menstruation, more children, or longer exposure to HRT might protect against AMD. Early menopause before age 45 years has a relative risk (RR) of 1.9 for lAMD (Vingerling et al. 1995). HRT protected against wAMD in a clinic-based case–control study, and having one or more children was a risk factor (EDCCSG 1992). In a population-based 5-year incidence study, HRT had no effect (Klein et al. 2000). A cross-sectional population-based study and in India found that older age at menarche elevated the risk of AMD (Nirmalan et al. 2004). In this study, only 3 % of the women had AMD, and although the international classification was only intended for classification on fundus images (Bird et al. 1995), the AMD diagnosis here was reached by ophthalmoscopy. In an RCT with estrogens or estrogens plus progestin on women aged 65 years and over, the AMD, prevalence was 21 %, but there were only 20 wAMD cases in the 2,635 taking also progestin. The conclusion was that estrogen plus progestin might protect against any soft drusen and wAMD (Haan et al. 2006). Estrogens mediate their effects through intracellular receptors *ESR1* and *ESR2*. The *ESR1 Pvu*II-*Xha*I haplotype 1 had after a mean follow-up up of 7.7 years in heterozygous persons a 3.7 higher risk of wAMD, and in homozygous persons, this was 4.7 (95 % CI 1.62–13.66) (Boekhoorn et al. 2007). So HRT seems not to be a major protective factor against AMD, and genetic combinations may evolve in due course, in combination with HRT, to carry a higher risk. A meta-analysis found no link between female gender and lAMD (Chakravarthy et al. 2010), but there is some evidence that women have a slightly higher risk of wAMD (Rudnicka et al. 2012).

#### 4.3.3.8 Kidney Function (Reduced)

There are some reports on links between reduced kidney function and eAMD or wAMD (Liew et al. 2008; Klein et al. 2009; Nitsch et al. 2009; Weiner et al. 2011; Choi et al. 2011). They are partially contradictory. Some kidney diseases seem to be associated with white flecks in the retina (Duvall-Young et al. 1989), and it remains questionable whether those flecks may be considered to be drusen and have led to misclassification of eAMD (Table 4.3).

#### 4.3.3.9 Light Exposure (Elevated)

To confirm or deny the influence of light exposure on AMD as in cataract is difficult, if only because of the problems involved in obtaining reliable information on lifetime exposure, measuring its radiation levels, and changing views on retinal phototoxicity (Hunter et al. 2012). There is no connection between UVB or blue light and AMD (West et al. 1989b; Fletcher et al. 2008), but the latter cross-sectional population-based study found significant links with wAMD in participants who also had the lowest quartile of antioxidant serum levels.

#### 4.3.3.10 Medicines, Nutrients, and Supplements (Risk or Protective)

##### Medicines Associated with AMD

###### Statins

A cross-sectional study in participants from a hospital registry suggested a protective effect of statin use (Hall et al. 2001). A cross-sectional population-based study found a low number (30) of lAMD cases. Angiotensin-converting enzyme inhibitors or ever having taken cholesterol-lowering

medication elevated their risk of lAMD (McCarty et al. 2001). In prospective studies, statin use either did not protect (van Leeuwen et al. 2001; Klein et al. 2007b) or only protected against eAMD in one study with 7 % statin users and one case of lAMD (Tan et al. 2007). Cochrane could not find studies suitable for analysis of statins and AMD (Gehlbach et al. 2009).

#### Aspirin

In a cross-sectional population-based study, daily aspirin intake increased the risk of wAMD (de Jong et al. 2012) in contrast to earlier RCTs (Christen et al. 2001, 2009). This is mentioned here only because of the widespread use of aspirin as primary and secondary prevention for CaVD and CeVD. In the pooled analysis of three population-based cohort studies, aspirin was not analyzed because less than 2 % of the baseline population mentioned aspirin use (Tomany et al. 2004). However, one longitudinal population-based study found a HR 2.2 (CI 1.2–4.15) for nAMD in persons who regularly took aspirin for 10 years (Klein et al. 2012) and in another study with 15 years follow-up the OR for nAMD was 2.46 (1.25–4.83) (Liew et al. 2013). This warrants caution for aspirin as primary prevention of CaVD in persons with any AMD.

#### Antioxidant Intake (Low), Carotenoids as Lutein and Zeaxanthin

Dietary studies often have a problem of recall bias when asking what food people were eating over a certain period in the past. That may be one reason for controversial outcomes. One population-based cross-sectional study found that vitamin A but not vitamin C protected against AMD (Goldberg et al. 1988), while a clinic-based case–control study found the opposite to be the case (Seddon et al. 1994). The latter study mentioned the carotenoids lutein and zeaxanthin as being protective. A population-based cohort study mentioned modest protection by provitamin A and vitamin E for eAMD and by zinc against pigmentary abnormalities, but had power problems to look at lAMD (VandenLangenberg et al. 1998). Later similar observational studies confirmed stronger protective effects of antioxidants on AMD (van Leeuwen et al. 2005; Tan et al. 2008a), but a review of six of these cohort studies could not find any significant effect (Ma et al. 2012). A RCT found a protective effect of antioxidants plus zinc after excluding mild eAMD cases (Age-Related Eye Disease Study Research Group 2001)

A Cochrane review examined three RCTs with alpha-tocopherol and beta-carotene supplements and concluded: “There was no evidence that antioxidant vitamin supplementation prevented or delayed the onset of AMD” (Evans and Henshaw 2009). Another non-US review even mentioned a higher mortality risk in those taking supplements (Gerding and Thelen 2010).

## 4.4 Risk Factors for Primary Open-Angle Glaucoma (POAG)

Glaucoma is a collective term for poorly understood disorders in retinal neurons. The neuronal cell death results in loss of retinal nerve fibers. This nerve fiber loss may become clinically manifest in red-free retinal images, nerve fiber layer thinning, increased cupping of the optic nerve head leading to a larger (vertical) cup-to-disc ratio (VCDR), glaucomatous visual field loss (GVFL) or a combination of these. However, this holds more for (primary) open-angle glaucoma ((P)OAG) than for (acute) angle-closure glaucoma, the latter being in some parts of the world more prevalent than POAG.

The classification of POAG seems to be an even greater problem than in AMD or cataract. In the same population-based data set, the prevalence of POAG rose from 0.6 to 5.8 % (nearly ten times higher) in participants aged 80 years or over, simply by applying different diagnostic criteria from six more population-based studies (Wolfs et al. 2000)! The Framingham Eye Study had a two-step procedure with visual field (VF) examination only in referred cases, before a diagnosis of POAG could be reached (Kahn et al. 1977). Participants had OAG when one of five GVFL criteria was present, “provided there was no definite or doubtful diagnosis of acute, secondary, or other than open-angle glaucoma for the same eye.” When a person was not referred for definite examination, OAG was negative. Wolfs only made a diagnosis of

**Table 4.4** Examples of secondary open-angle glaucoma

| Cause | Examples | Subgroups/examples |
|---|---|---|
| Developmental | Aniridia | |
| | Iridocorneo-endothelial syndrome | |
| | Peters anomaly | |
| Elevated venous pressure | Cavernous sinus | Fistula, thrombosis |
| | Nevus flammeus | Sturge-Weber disease |
| Inflammatory | Uveitis | |
| | Bacterial/viral infection | Herpes zoster |
| | | Syphilis |
| Metabolic disturbances | Amyloidosis | |
| | Cystinosis | |
| | Mucopolysaccharidosis | |
| Multi organ/system syndromes | Graves disease | |
| | Lymphoma | |
| | Phakomatosis | |
| Neovascular glaucoma | Diabetes mellitus | |
| | Central retinal vein occlusion | |
| Intraocular tumors | Melanoma, metastasis | |
| Trauma | | |
| Chemical | Acid or lye burns | Corticosteroids |
| | Medicine use | |
| Physical | Contusion of eye | |
| | Hyphema | |
| | Irradiation | Ionizing |
| | Perforation of eye | Foreign body |
| | Surgery | |

Excluding congenital glaucoma (buphthalmos) and chronic angle-closure glaucoma

definite POAG based on the presence of glaucomatous optic neuropathy (GON) in combination with GVFL that implies exclusion of other causes for VF loss, without intraocular pressure (IOP) as a diagnostic criterion. In this chapter, normotensive (NT) OAG (ntOAG) refers to an IOP that was found never to be over 21 mmHg in a diurnal curve; otherwise, the term ocular hypertension (OHT) is used. There are only a few population-based POAG incidence studies. Statistical power problems were encountered in these more often than in AMD because of the lower incidence of POAG.

As is the case with aging cataract, whenever we discover a cause for OAG, that part of OAG cannot be called primary anymore. Another similarity is that, clinically, we divide OAG into primary and secondary. In Table 4.4, some examples of secondary OAG are given. Risk factors of POAG are provided in alphabetical order; its genetic background will be discussed in the next chapter.

### 4.4.1 Risk Factors: Evidence Level I

#### 4.4.1.1 Age

An extrapolation of data from eight population-based case–control and cohort studies estimated the prevalence of POAG in the USA in black women (men) between ages 40 and 49 years to be 1.51% (0.55)%. This was 0.34 (0.39)% for Hispanics and 0.83 (0.36)% for whites. Above the age of 80, these prevalences were 9.82 (13.21)% in blacks, 10.05 (7.91)% in Hispanics, and 6.94 (5.58)% in whites (Friedman et al. 2004b). This would point to a rise in prevalence of 6.5 times in elderly black women and to a prevalence of 29 times higher in old

Hispanic men. Smaller rises (2–3×) with aging were seen in China (Song et al. 2011) and India (4×) (Vijaya et al. 2008). Age was a risk factor in all cohort studies (Mukesh et al. 2002; Leske et al. 2008; Czudowska et al. 2010; Cedrone et al. 2012).

#### 4.4.1.2 Ethnicity

Blacks have a (4–5×) higher prevalence of POAG than whites both in a clinic-based screening program (Packer et al. 1959) and in a nonrepresentative population screening (Frydman et al. 1966; Coulehan et al. 1980). This held also for population-based prevalence studies (4–5×) (Tielsch et al. 1991; Rotchford et al. 2003) (2×) (Friedman et al. 2006) and cohort studies (3–6×) (Leske et al. 2007b; Czudowska et al. 2010). The prevalence in Hispanic persons lies between that of blacks and whites (Quigley et al. 2001). Because of differences in POAG classification and pooling of various glaucoma types, it was hard to tell what the prevalences of POAG in Chinese (Song et al. 2011), Indian (Vijaya et al. 2008), or Bangladesh (Rahman et al. 2004) populations are. Two studies found a similar prevalence between Chinese and Europeans (He et al. 2006; Wang et al. 2010b).

#### 4.4.1.3 Family History

Despite concerns as to how reliable a family history may be (Mitchell et al. 2002a), most studies that looked into it found a positive family history to be a risk factor for POAG (Leske et al. 2008; Sun et al. 2012). In one cohort study, family history only reached significance when IOP was left out of the analyses (Czudowska et al. 2010). When looking at family databases (Wang et al. 2010a) or actually examining family members (Wolfs et al. 1998; Hulsman et al. 2002), the family history is a clear risk factor.

#### 4.4.1.4 Glaucomatous Optic Neuropathy (GON) or Vertical Cup-to-Disc Ratio (VCDR)

The diagnosis GON is mostly made on the basis of arbitrary cutoff points of horizontal or vertical cup-to-disc ratios or local thinning (notching) of the rim of the cup (Wolfs et al. 2000). Most population-based incidence studies showed that a VCDR ≥ 0.7 was a risk factor for POAG (Mukesh et al. 2002; Leske et al. 2007b; Czudowska et al. 2010), but one study failed to do so (Cedrone et al. 2012). One should take care in the study design not to confuse a diagnostic criterion for POAG with a risk factor for it.

#### 4.4.1.5 Intraocular Pressure (IOP)

That elevated IOP is associated with POAG is known for ages (Donders 1864; Packer et al. 1959; Armaly and Sayegh 1969). The methodology for measuring the IOP as accurately as possible has been extensively studied (Goldmann and Schmidt 1957; Armaly and Salamoun 1963; Perkins 1967; Dielemans et al. 1994), but there is a still wide variation in applanation and indentation techniques. After a wide-ranging search through the literature and extensive testing, the most reliable measuring technique for IOP in epidemiological studies seems to be the median of three applanation tonometry measurements under specific conditions (Dielemans et al. 1994). Even in experienced hands a fluctuation of 2–3 mmHg can easily occur at a certain time point. In a cross-sectional clinic-based study, morning pressures were higher than later on the day as were IOPs in the pre-ovulation days in women (Bankes et al. 1968). Despite the relative inaccuracy of IOP measurements, an elevated IOP is one of the strongest risk factors for POAG both in prevalence (Hollows and Graham 1966; Kahn et al. 1977; Bengtsson 1981; Sommer et al. 1991) and incidence studies (Mukesh et al. 2002; Leske et al. 2007b; Czudowska et al. 2010; Cedrone et al. 2012). The HR for incident GVFL per mm higher IOP at baseline was 1.11 (CI 1.06–1.15) (Czudowska et al. 2010).

#### 4.4.1.6 Refraction

Myopia is a risk factor in most prevalence studies, and the OR for POAG between −1.0 D and 3.0 D was 2.3 and ≥3.0 D was 3.3 (Mitchell et al. 1999) (cf. the overview of 11 cross-sectional population-based studies in which the ORs below −3.0 D for POAG were 1.65 and ≥ −3.0 D were 2.46) (Marcus et al. 2011). There seems to be only one population-based incidence study with data on refraction that also found that myopia was a risk factor (Czudowska et al. 2010). Longer axial length by itself was also a risk factor (Sia et al. 2010; Kuzin et al. 2010) as was a flatter cornea in the latter study.

### 4.4.2 Risk Factors: Evidence Level II

#### 4.4.2.1 Disc Hemorrhages

Disc hemorrhages come and go (Drance and Begg 1970), and it was mentioned that one would need monthly examinations to catch them all (Drance 1989). Despite the fact that they can easily be missed and that their origin is poorly understood, their significance as a risk factor for GVFL has been well documented for a long time in clinic-based (Drance and Begg 1970) and population-based studies (Ekstrom 1993). A clinic-based study found a higher risk of GVFL associated with disc hemorrhages in NT than HT POAG (Rasker et al. 1997). Hemorrhages, however, occur in about 1.4 % of the white population over 49 years old, and 70 % of these eyes had no POAG. Of the 108 POAG cases in a cross-sectional population-based study, 13.8 % had disc hemorrhages, and these were three times more prevalent in NT POAG (Healey et al. 1998). This study found a low sensitivity of disc hemorrhages for POAG, about 13 %, and a high specificity of 99 %. In a clinical trial cohort, the HR for OAG progression was 1.02 (CI 1.01–1.03) per percent higher frequency of visits in which disc hemorrhages were found (Leske et al. 2007a).

### 4.4.3 Risk Factors: Evidence Level III or Lower

#### 4.4.3.1 Alcohol

Alcohol intake seems hardly a risk factor for POAG, unless huge amounts of beer are consumed daily, simulating the old water-loading test from the 1960s (Xu et al. 2009; Ramdas et al. 2011a).

#### 4.4.3.2 Blood (BP) (Elevated) and Perfusion Pressure (PeP) (Lowered)

The association between elevated systolic and diastolic blood pressure (BP) and glaucoma was noted over 100 years ago. It seems that various forms of glaucoma were pooled in that clinical study (Kuemmell 1911). Associations between elevated BP and elevated IOP later became known (Leighton and Phillips 1972; Kahn et al. 1977) and were confirmed in many population-based cohort studies (Klein et al. 2005). Systemic hypertension was associated with POAG in population-based cross-sectional studies (Dielemans et al. 1995; Bonomi et al. 2000; Mitchell et al. 2004). Because of power problems, systemic hypertension was not confirmed as a risk factor in the follow-up to one of these (Hulsman et al. 2007). Elevated PeP (2/3 mean arterial BP–IOP) was a risk factor for high tension (HT) OAG but not for NT OAG. A low diastolic PeP was a risk for both NT and HT OAG (Hulsman et al. 2007). Recently, it was concluded from a population-based cohort study that the ocular PeP is a risk factor for POAG but mainly because IOP (another important risk factor) is also incorporated into the PeP (Ramdas et al. 2011b). Overall systemic hypertension seems to be an inconsistent risk factor for OAG, but diastolic hypotension might be a factor (Leske et al. 2007b, 2008; Leske 2009).

#### 4.4.3.3 Central Corneal Thickness (CCT)

That corneal parameters could influence the exact measurement of the IOP has been known for about 150 years (Donders 1863; Goldmann and Schmidt 1957). The CCT can be measured with an optical tachymeter or an ultrasonic device, the former giving on average 4 μm (Doughty and Zaman 2000) lower values. The CCT was independent of sex and age in a cross-sectional population-based study and was 16 μm thicker in ocular hypertension and 21.5 μm thinner in POAG cases (Wolfs et al. 1997). Another similar study, in Mongolia, found a 5 μm decrease per decade of aging in men and 6 μm in women; a 10 μm increase in CCT was associated with a 0.21 mmHg increase in IOP (Foster et al. 1998). Age seems not to play a role on CCT in whites but does so in nonwhites (Doughty and Zaman 2000) and was on average 17 μm lower in African-Americans (Shimmyo et al. 2003). In the UK, no relation between CCT and age was found (Foster et al. 2011). The CCT was not associated with POAG in 938 population-derived participants but was so in 243 hospital-derived POAG cases, possibly due to the low number of POAG cases in the community (Day et al. 2011). A Japanese population-based prevalence study found no link between CCT and POAG (Iwase et al. 2004) nor

did a Malay (Perera et al. 2010) or a Chinese one (Wang et al. 2011). A thinner CCT was a risk factor in a population-based cohort study (Leske et al. 2008). The CCT increases at higher altitude (Morris et al. 2007). Care should be taken when considering lower CCT as a risk factor for POAG, given the complexity of CCT variables which are influenced by changes caused by age, eye or collagen disorders, IOP, and altitude.

#### 4.4.3.4 Diabetes Mellitus

Diabetes is often mentioned as a risk factor for POAG. Diabetes may create secondary OAG due to neovascular glaucoma, glaucoma after a complicated cataract extraction or after infection; those are considered to be secondary OAG. Diabetes was not a risk factor for POAG in two cross-sectional population-based studies (Tielsch et al. 1995; Tarkkanen et al. 2008) nor in such an incidence study (de Voogd et al. 2006).

#### 4.4.3.5 Education

One population-based prevalence study from Singapore mentioned that persons with lower education and income had a higher mean IOP (Yip et al. 2007), but this could not be confirmed either in a cohort study of blacks (Leske et al. 2008) or one of whites (Ramdas et al. 2011a).

#### 4.4.3.6 Glaucomatous Visual Field Loss (GVFL)

Glaucomatous visual field loss should be considered more as sign of definite POAG than a risk factor. The prevalence of any VFL in the general population was 3 % between the ages of 55–64 and 17 % over age 85. POAG was the leading cause in 27 % of the eyes (Ramrattan et al. 2001) as it was in 24 % of eyes with incident VFL (Skenduli-Bala et al. 2005).

#### 4.4.3.7 Sex, Early Menopause, and Hormone Replacement Therapy (HRT)

Sex as a risk factor is controversial from the first documented higher prevalence in women in a clinic-based study (Haffmans 1861). Menopause before age 45 was associated with OAG (Hulsman et al. 2001), and haplotype 1 of the estrogen receptor beta was a risk factor for POAG in men (de Voogd et al. 2008) and for a high IOP in clinic-derived Japanese women (Mabuchi et al. 2010), although they seemed not to check the time of measuring the IOP during the menstrual cycle (Bankes et al. 1968). One population-based white Australian cohort study found a nonsignificant higher incidence of POAG in men (Mukesh et al. 2002) as did a study in Italy (Cedrone et al. 2012); two Swedish studies mentioned a twice higher incidence in women (Bengtsson 1989; Ekström 2008), while large cohort studies found a higher risk in black (Leske et al. 2007b) and white men (Czudowska et al. 2010). Given this controversial data across various ethnicities, sex does not appear to be a definite universal risk factor.

#### 4.4.3.8 Smoking

Hardly any incidence studies looked at smoking. There was a slightly positive association between smoking and IOP (Lee et al. 2003), but smoking was not a risk factor in a large population-based cohort study (Ramdas et al. 2011a).

#### 4.4.3.9 Vascular

There is extensive literature on vascular risk factors for POAG (Grieshaber et al. 2007) or autonomous dysregulation, but, in my view, most of this depends on circumstantial evidence. As may be clear from my comments on BP, PeP, and diabetes, there is still much uncertain or controversial in the vascular origin of POAG. The reader is referred to a wide-ranging review of this matter (Yanagi et al. 2011).

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Age-Related Eye Disease Study Research Group (2001) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 119(10): 1439–1452

Ajani UA et al (1999) A prospective study of alcohol consumption and the risk of age-related macular degeneration. Ann Epidemiol 9(3):172–177

Armaly MF, Salamoun SG (1963) Schiotz and applanation tonometry. Arch Ophthalmol 70:603–609
Armaly MF, Sayegh RE (1969) The cup-disc ratio. The findings of tonometry and tonography in the normal eye. Arch Ophthalmol 82(2):191–196
Arnarsson A et al (2002) Risk factors for nuclear lens opacification: the Reykjavik Eye Study. Dev Ophthalmol 35:12–20
Arnarsson A et al (2006) Risk factors for five-year incident age-related macular degeneration: the Reykjavik Eye Study. Am J Ophthalmol 142(3):419–428
Athanasiov PA et al (2008) Cataract in rural Myanmar: prevalence and risk factors from the Meiktila Eye Study. Br J Ophthalmol 92(9):1169–1174
Augood C et al (2008) Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr 88(2):398–406
Bankes JL et al (1968) Bedford glaucoma survey. Br Med J 1(5595):791–796
Bengtsson B (1981) The prevalence of glaucoma. Br J Ophthalmol 65(1):46–49
Bengtsson BO (1989) Incidence of manifest glaucoma. Br J Ophthalmol 73(7):483–487
Bird AC et al (1995) An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol 39(5): 367–374
Boekhoorn SS et al (2007) Estrogen receptor alpha gene polymorphisms associated with incident aging macula disorder. Invest Ophthalmol Vis Sci 48(3):1012–1017
Boekhoorn SS et al (2008) Alcohol consumption and risk of aging macula disorder in a general population: the Rotterdam Study. Arch Ophthalmol 126(6):834–839
Bonomi L et al (2000) Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology 107(7):1287–1293
Bressler SB et al (2008) Racial differences in the prevalence of age-related macular degeneration: the Salisbury Eye Evaluation (SEE) Project. Arch Ophthalmol 126(2):241–245
Brilliant LB et al (1983) Associations among cataract prevalence, sunlight hours, and altitude in the Himalayas. Am J Epidemiol 118(2):250–264
Cackett P et al (2008) Smoking, cardiovascular risk factors, and age-related macular degeneration in Asians: the Singapore Malay Eye Study. Am J Ophthalmol 146(6):960–967
Casparis H, Lindsley K, Bressler NB (2009) Surgery for cataracts in people with age-related macular degeneration. Cochrane Database Syst Rev (1):CD006757
Cedrone C et al (2012) The 12-year incidence of glaucoma and glaucoma-related visual field loss in Italy: the Ponza eye study. J Glaucoma 21(1):1–6
Chakravarthy U et al (2010) Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 10:31
Chang JR et al (2011) Risk factors associated with incident cataracts and cataract surgery in the Age-related Eye Disease Study (AREDS): AREDS report number 32. Ophthalmology 118(11):2113–2119
Cheung N, Wong TY (2007) Obesity and eye diseases. Surv Ophthalmol 52(2):180–195
Cheung CM et al (2011) Retinal arteriolar wall signs and early age-related macular degeneration: the Singapore Malay Eye Study. Am J Ophthalmol 152(1): 108–113
Cheung CMG, Tai ES, Kawasaki R et al (2012) Prevalence of and risk factors for age-related macular degeneration in a multiethnic Asian cohort. Arch Ophthalmol 130(4):480–486
Chew H et al (2005) Socioeconomic status and clinical features of patients undergoing photodynamic therapy or transpupillary thermotherapy for subfoveal choroidal neovascularization due to age-related macular degeneration. Can J Ophthalmol 40(3):384–388
Chew EY et al (2010) Evaluation of the age-related eye disease study clinical lens grading system AREDS report no. 31. Ophthalmology 117(11):2112–2119
Chiu CJ, Taylor A (2007) Nutritional antioxidants and age-related cataract and maculopathy. Exp Eye Res 84(2):229–245
Cho E et al (2001) Prospective study of dietary fat and the risk of age-related macular degeneration. Am J Clin Nutr 73(2):209–218
Choi J, Moon JW, Shin HJ (2011) Chronic kidney disease, early age-related macular degeneration, and peripheral retinal drusen. Ophthalmic Epidemiol 18(6): 259–263
Chong EW et al (2008a) Alcohol consumption and the risk of age-related macular degeneration: a systematic review and meta-analysis. Am J Ophthalmol 145(4): 707–715
Chong EW et al (2008b) Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. Arch Ophthalmol 126(6):826–833
Choudhury F et al (2011) Risk factors for four-year incidence and progression of age-related macular degeneration: the los angeles latino eye study. Am J Ophthalmol 152(3):385–395
Christen WG et al (1992) A prospective study of cigarette smoking and risk of cataract in men. JAMA 268(8): 989–993
Christen WG et al (2001) Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. Arch Ophthalmol 119(8):1143–1149
Christen WG et al (2009) Low-dose aspirin and medical record-confirmed age-related macular degeneration in a randomized trial of women. Ophthalmology 116(12):2386–2392
Chua B et al (2006) Dietary fatty acids and the 5-year incidence of age-related maculopathy. Arch Ophthalmol 124(7):981–986
Chylack LT Jr et al (1988) Lens opacities classification system. Arch Ophthalmol 106(3):330–334
Chylack LT Jr et al (2009) NASA study of cataract in astronauts (NASCA). Report 1: cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. Radiat Res 172(1):10–20

Congdon N et al (2004) Prevalence of cataract and pseudophakia/aphakia among adults in the United States. Arch Ophthalmol 122(4):487–494
Coulehan JL et al (1980) Racial differences in intraocular tension and glaucoma surgery. Am J Epidemiol 111(6):759–768
Cugati S et al (2006) Cataract surgery and the 10-year incidence of age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology 113(11):2020–2025
Czudowska MA et al (2010) Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. Ophthalmology 117(9):1705–1712
Day AC et al (2011) Central corneal thickness and glaucoma in East Asian people. Invest Ophthalmol Vis Sci 52(11):8407–8412
de Jong PT (2011) Reflections on "hot" blind spots: lessons from research on aging macula disorder and glaucoma: the Weisenfeld lecture. Invest Ophthalmol Vis Sci 52(10):7717–7724, 7716
de Jong PT et al (2012) Associations between aspirin use and aging macula disorder: the European Eye Study. Ophthalmology 119(1):112–118
de Voogd S et al (2006) Is diabetes mellitus a risk factor for open-angle glaucoma? The Rotterdam Study. Ophthalmology 113(10):1827–1831
de Voogd S et al (2008) Estrogen receptors alpha and beta and the risk of open-angle glaucoma: the Rotterdam Study. Arch Ophthalmol 126(1):110–114
Dielemans I et al (1994) Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies. Graefes Arch Clin Exp Ophthalmol 232(3):141–144
Dielemans I et al (1995) Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. Ophthalmology 102(1):54–60
Donders FC (1863) Vorzeigung neuer, ophthalmometrischer Instrumente; (Ophthalmo) tonometer. (Demonstration of new ophthalmometric instruments: (Ophthalmo) tonometer). Klin Monbl Augenheilkd 1:1502–1504
Donders FC (1864) Ueber Glaucom (On glaucoma). Klin Monbl Augenheilkd 2:433–437
Doughty MJ, Zaman ML (2000) Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol 44(5):367–408
Drance SM (1989) Disc hemorrhages in the glaucomas. Surv Ophthalmol 33(5):331–337
Drance SM, Begg IS (1970) Sector haemorrhage – a probable acute ischaemic disc change in chronic simple glaucoma. Can J Ophthalmol 5(2):137–141
Duke-Elder S (1964) System of ophthalmology, vol III, Normal and abnormal development, part 2, congenital deformities. Henry Kimpton, London
Duvall-Young J, MacDonald MK, McKechnie NM (1989) Fundus changes in (type II) mesangiocapillary glomerulonephritis simulating drusen: a histopathological report. Br J Ophthalmol 73(4):297–302
Ekstrom C (1993) Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open-angle glaucoma. A population-based five-year follow-up study. Acta Ophthalmol (Copenh) 71(2):189–195
Ekström C (2008) Incidence of open-angle glaucoma in central Sweden. Acta Ophthalmol 86(7):747–754
Evans J, Henshaw K (2009) Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (review). Cochrane Database Syst Rev (1):CD000253
Fernandez AB et al (2012) Age-related macular degeneration and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. Ophthalmology 119:765–770
Flaye DE et al (1989) Cataracts and cigarette smoking. The City Eye Study. Eye (Lond) 3(Pt 4):379–384
Fletcher AE et al (2008) Sunlight exposure, antioxidants, and age-related macular degeneration. Arch Ophthalmol 126(10):1396–1403
Foster PJ et al (1998) Central corneal thickness and intraocular pressure in a Mongolian population. Ophthalmology 105(6):969–973
Foster PJ et al (2011) Intraocular pressure and corneal biomechanics in an adult British population: the EPIC-Norfolk eye study. Invest Ophthalmol Vis Sci 52(11):8179–8185
Fotedar R et al (2008) Relationship of 10-year change in refraction to nuclear cataract and axial length findings from an older population. Ophthalmology 115(8): 1273–1278, 1278
Fraser-Bell S et al (2005) Sociodemographic factors and age-related macular degeneration in Latinos: the Los Angeles Latino Eye Study. Am J Ophthalmol 139(1):30–38
Fraser-Bell S et al (2008) Cardiovascular risk factors and age-related macular degeneration: the Los Angeles Latino Eye Study. Am J Ophthalmol 145(2):308–316
Fraser-Bell S et al (2010) Ocular risk factors for age-related macular degeneration: the Los Angeles Latino Eye Study. Am J Ophthalmol 149(5):735–740
Freeman EE et al (2003) Is there an association between cataract surgery and age-related macular degeneration? Data from three population-based studies. Am J Ophthalmol 135(6):849–856
Freeman EE et al (2004) Incidence and progression of lens opacities: effect of hormone replacement therapy and reproductive factors. Epidemiology 15(4):451–457
Friedman DS et al (1999) Racial differences in the prevalence of age-related macular degeneration: the Baltimore Eye Survey. Ophthalmology 106(6):1049–1055
Friedman DS et al (2004a) Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 122(4):564–572
Friedman DS et al (2004b) Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol 122(4):532–538
Friedman DS et al (2006) The prevalence of open-angle glaucoma among blacks and whites 73 years and older: the Salisbury Eye Evaluation Glaucoma Study. Arch Ophthalmol 124(11):1625–1630
Frydman JE et al (1966) Glaucoma detection in Florida. JAMA 198(12):1237–1240

Gehlbach P, Li T, Hatef E (2009) Statins for age-related macular degeneration. Cochrane Database Syst Rev (3):CD006927

Gerding H, Thelen U (2010) Primary and secondary prophylaxis of AMD by antioxidants: current risk-benefit data. Klin Monbl Augenheilkd 227(4):298–301

Goldberg J et al (1988) Factors associated with age-related macular degeneration. An analysis of data from the first National Health and Nutrition Examination Survey. Am J Epidemiol 128(4):700–710

Goldmann H, Schmidt T (1957) Ueber Applanationstonometrie. Ophthalmologica 134:221–242

Grieshaber MC, Mozaffarieh M, Flammer J (2007) What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol 52(Suppl 2):S144–S154

Gudmundsdottir E, Arnarsson A, Jonasson F (2005) Five-year refractive changes in an adult population: Reykjavik Eye Study. Ophthalmology 112(4):672–677

Guzowski M et al (2003) Five-year refractive changes in an older population: the Blue Mountains Eye Study. Ophthalmology 110(7):1364–1370

Haan MN et al (2006) Hormone therapy and age-related macular degeneration: the Women's Health Initiative Sight Exam Study. Arch Ophthalmol 124(7): 988–992

Haffmans JHA (1861) Beiträge zur Kenntniss des Glaucoms. Archiv für Ophthalmologie 8:124–178

Hall NF et al (2001) Risk of macular degeneration in users of statins: cross sectional study. BMJ 323(7309): 375–376

Hammond CJ et al (2000) Genetic and environmental factors in age-related nuclear cataracts in monozygotic and dizygotic twins. N Engl J Med 342(24):1786–1790

Hammond CJ et al (2001) The heritability of age-related cortical cataract: the twin eye study. Invest Ophthalmol Vis Sci 42(3):601–605

Hankinson SE et al (1992) A prospective study of cigarette smoking and risk of cataract surgery in women. JAMA 268(8):994–998

He M et al (2006) Prevalence and clinical characteristics of glaucoma in adult Chinese: a population-based study in Liwan District, Guangzhou. Invest Ophthalmol Vis Sci 47(7):2782–2788

Healey PR et al (1998) Optic disc hemorrhages in a population with and without signs of glaucoma. Ophthalmology 105(2):216–223

Hill AB (1965) The environment and disease: association or causation? Proc R Soc Med 58(5):295–300

Ho L et al (2008) Cataract surgery and the risk of aging macula disorder: the Rotterdam study. Invest Ophthalmol Vis Sci 49(11):4795–4800

Ho L et al (2011) Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and omega-3 fatty acids: the Rotterdam study. Arch Ophthalmol 129(6):758–766

Hockwin O (1994) Cataract classification. Doc Ophthalmol 88(3–4):263–275

Hodge WG, Whitcher JP, Satariano W (1995) Risk factors for age-related cataracts. Epidemiol Rev 17(2): 336–346

Hollows FC, Graham PA (1966) Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 50(10):570–586

Hollows F, Moran D (1981) Cataract – the ultraviolet risk factor. Lancet 2(8258):1249–1250

Hulsman CA et al (2001) Is open-angle glaucoma associated with early menopause? The Rotterdam Study. Am J Epidemiol 154(2):138–144

Hulsman CA et al (2002) Family score as an indicator of genetic risk of primary open-angle glaucoma. Arch Ophthalmol 120(12):1726–1731

Hulsman CA et al (2007) Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. Arch Ophthalmol 125(6):805–812

Hunter JJ et al (2012) The susceptibility of the retina to photochemical damage from visible light. Prog Retin Eye Res 31(1):28–42

Hyman LG et al (1983) Senile macular degeneration: a case–control study. Am J Epidemiol 118(2): 213–227

Ikram MK et al (2003) Relationship between refraction and prevalent as well as incident age-related maculopathy: the Rotterdam Study. Invest Ophthalmol Vis Sci 44(9):3778–3782

Ikram MK et al (2005) Retinal vessel diameters and the risk of incident age-related macular disease: the Rotterdam Study. Ophthalmology 112(4):548–552

Iwase A et al (2004) The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 111(9):1641–1648

Javitt JC, Taylor HR (1994) Cataract and latitude. Doc Ophthalmol 88(3–4):307–325

Jeganathan VS et al (2008) Retinal vascular caliber and age-related macular degeneration: the Singapore Malay Eye Study. Am J Ophthalmol 146(6): 954–959

Kahn HA et al (1977) The Framingham Eye Study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham Heart Study. Am J Epidemiol 106(1):33–41

Kanthan GL et al (2010) Exogenous oestrogen exposure, female reproductive factors and the long-term incidence of cataract: the Blue Mountains Eye Study. Acta Ophthalmol 88(7):773–778

Karppi J, Laukkanen JA, Kurl S (2012) Plasma lutein and zeaxanthin and the risk of age-related nuclear cataract among the elderly Finnish population. Br J Nutr 108:148–154

Kawasaki R et al (2008) Prevalence and risk factors for age-related macular degeneration in an adult Japanese population: the Funagata study. Ophthalmology 115(8):1376–1381, 1381

Klaver CC et al (1998) Genetic risk of age-related maculopathy. Population-based familial aggregation study. Arch Ophthalmol 116(12):1646–1651

Klein R et al (1998) The relationship of ocular factors to the incidence and progression of age-related maculopathy. Arch Ophthalmol 116(4):506–513

Klein BE, Klein R, Lee KE (2000) Reproductive exposures, incident age-related cataracts, and age-related

maculopathy in women: the Beaver Dam Eye Study. Am J Ophthalmol 130(3):322–326
Klein R et al (2002) Ten-year incidence of age-related maculopathy and smoking and drinking: the Beaver Dam Eye Study. Am J Epidemiol 156(7):589–598
Klein BE, Klein R, Knudtson MD (2005) Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. Br J Ophthalmol 89(3):284–287
Klein R et al (2006) Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. Ophthalmology 113(3):373–380
Klein BE, Klein R (2007) Lifestyle exposures and eye diseases in adults. Am J Ophthalmol 144(6):961–969
Klein R et al (2007a) Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: Women's Health Initiative Sight Exam ancillary study. Am J Ophthalmol 143(3):473–483
Klein R, Knudtson MD, Klein BE (2007b) Statin use and the five-year incidence and progression of age-related macular degeneration. Am J Ophthalmol 144(1):1–6
Klein R et al (2008) The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. Am J Ophthalmol 146(5):692–699
Klein R et al (2009) Serum cystatin C level, kidney disease markers, and incidence of age-related macular degeneration: the Beaver Dam Eye Study. Arch Ophthalmol 127(2):193–199
Klein BEK, Kerri PH, Gangnon RE, Dreyer JO, Lee KE, Klein R (2012) Long-term use of aspirin and age-related macular degeneration. JAMA 308(23): 2469–2478
Knudtson MD, Klein R, Klein BE (2007) Alcohol consumption and the 15-year cumulative incidence of age-related macular degeneration. Am J Ophthalmol 143(6):1026–1029
Krishnaiah S et al (2005a) Risk factors for age-related macular degeneration: findings from the Andhra Pradesh eye disease study in South India. Invest Ophthalmol Vis Sci 46(12):4442–4449
Krishnaiah S et al (2005b) Smoking and its association with cataract: results of the Andhra Pradesh eye disease study from India. Invest Ophthalmol Vis Sci 46(1):58–65
Kuemmell R (1911) Untersuchungen ueber Glaukom und Blutdruck (Investigations on glaucoma and blood pressure). Albr v Graefe's Archiv fuer Ophthalmologie 74(2):183–209
Kuzin AA et al (2010) Ocular biometry and open-angle glaucoma: the Los Angeles Latino Eye Study. Ophthalmology 117(9):1713–1719
Lavanya R et al (2010) Hyperopic refractive error and shorter axial length are associated with age-related macular degeneration: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci 51(12):6247–6252
Lee KE, Klein BE, Klein R (1999) Changes in refractive error over a 5-year interval in the Beaver Dam Eye Study. Invest Ophthalmol Vis Sci 40(8):1645–1649
Lee AJ et al (2003) Does smoking affect intraocular pressure? Findings from the Blue Mountains Eye Study. J Glaucoma 12(3):209–212
Leibowitz HM et al (1980) The Framingham Eye Study monograph: an ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975. Surv Ophthalmol 24(Suppl):335–610
Leighton DA, Phillips CI (1972) Systemic blood pressure in open-angle glaucoma, low tension glaucoma, and the normal eye. Br J Ophthalmol 56(6):447–453
Leske MC (2009) Ocular perfusion pressure and glaucoma: clinical trial and epidemiologic findings. Curr Opin Ophthalmol 20(2):73–78
Leske MC, Sperduto RD (1983) The epidemiology of senile cataracts: a review. Am J Epidemiol 118(2): 152–165
Leske MC et al (2004) Nine-year incidence of lens opacities in the Barbados Eye Studies. Ophthalmology 111(3):483–490
Leske MC et al (2006) Nine-year incidence of age-related macular degeneration in the Barbados Eye Studies. Ophthalmology 113(1):29–35
Leske MC et al (2007a) Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology 114(11):1965–1972
Leske MC et al (2007b) Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. Ophthalmology 114(6):1058–1064
Leske MC et al (2008) Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology 115(1):85–93
Liew G et al (2006) Retinal vessel signs and 10-year incident age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology 113(9):1481–1487
Liew G et al (2008) CKD increases the risk of age-related macular degeneration. J Am Soc Nephrol 19(4): 806–811
Liew G, Mitchell P, Wong TY, Rochtchina E, Wang JJ (2013) The association of aspirin use with age-related macular degeneration. JAMA Intern Med 173(4): 258–264
Lim LS et al (2009) Relation of age-related cataract with obesity and obesity genes in an Asian population. Am J Epidemiol 169(10):1267–1274
Lindblad BE et al (2005) Intensity of smoking and smoking cessation in relation to risk of cataract extraction: a prospective study of women. Am J Epidemiol 162(1):73–79
Ma L et al (2012) Lutein and zeaxanthin intake and the risk of age-related macular degeneration: a systematic review and meta-analysis. Br J Nutr 107(3):350–359
Mabuchi F et al (2010) Estrogen receptor beta gene polymorphism and intraocular pressure elevation in female patients with primary open-angle glaucoma. Am J Ophthalmol 149(5):826–830
Maltzman BA, Mulvihill MN, Greenbaum A (1979) Senile macular degeneration and risk factors: a case–control study. Ann Ophthalmol 11(8):1197–1201

Marcus MW et al (2011) Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology 118(10):1989–1994

McCarty CA et al (2001) Risk factors for age-related maculopathy: the Visual Impairment Project. Arch Ophthalmol 119(10):1455–1462

McCarty CA et al (2008) Novel measures of cardiovascular health and its association with prevalence and progression of age-related macular degeneration: the CHARM Study. BMC Ophthalmol 8:25

Mitchell P et al (1999) The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology 106(10):2010–2015

Mitchell P et al (2002a) Bias in self-reported family history and relationship to glaucoma: the Blue Mountains Eye Study. Ophthalmic Epidemiol 9(5):333–345

Mitchell P et al (2002b) Smoking and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. Arch Ophthalmol 120(10):1357–1363

Mitchell P et al (2004) Open-angle glaucoma and systemic hypertension: the Blue Mountains Eye Study. J Glaucoma 13(4):319–326

Morris DS et al (2007) Corneal thickness at high altitude. Cornea 26(3):308–311

Mukesh BN et al (2002) Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology 109(6):1047–1051

Munoz B et al (2005) Prevalence of age-related macular degeneration in a population-based sample of Hispanic people in Arizona: Proyecto VER. Arch Ophthalmol 123(11):1575–1580

Nirmalan PK et al (2004) Female reproductive factors and eye disease in a rural South Indian population: the Aravind Comprehensive Eye Survey. Invest Ophthalmol Vis Sci 45(12):4273–4276

Nitsch D et al (2009) Associations between chronic kidney disease and age-related macular degeneration. Ophthalmic Epidemiol 16(3):181–186

Packer H et al (1959) Study of the frequency and distribution of glaucoma. J Am Med Assoc 171:1090–1093

Paetkau ME et al (1978) Senile disciform macular degeneration and smoking. Can J Ophthalmol 13(2):67–71

Patel JI (2007) Is cataract surgery a risk factor for progression of macular degeneration? Curr Opin Ophthalmol 18(1):9–12

Peeters A et al (2008) Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 126(11):1554–1560

Perera SA et al (2010) Refractive error, axial dimensions, and primary open-angle glaucoma: the Singapore Malay Eye Study. Arch Ophthalmol 128(7):900–905

Perkins ES (1967) Tonometry. Proc R Soc Med 60(1): 63–65

Piermarocchi S et al (2011) The prevalence of age-related macular degeneration in Italy (PAMDI) study: report 1. Ophthalmic Epidemiol 18(3):129–136

Quigley HA et al (2001) The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol 119(12):1819–1826

Rahman MM et al (2004) The prevalence of glaucoma in Bangladesh: a population based survey in Dhaka division. Br J Ophthalmol 88(12):1493–1497

Ramdas WD et al (2011a) Lifestyle and risk of developing open-angle glaucoma: the Rotterdam study. Arch Ophthalmol 129(6):767–772

Ramdas WD et al (2011b) Ocular perfusion pressure and the incidence of glaucoma: real effect or artifact? The Rotterdam Study. Invest Ophthalmol Vis Sci 52(9): 6875–6881

Ramrattan RS et al (2001) Prevalence and causes of visual field loss in the elderly and associations with impairment in daily functioning: the Rotterdam Study. Arch Ophthalmol 119(12):1788–1794

Rasker MT et al (1997) Deterioration of visual fields in patients with glaucoma with and without optic disc hemorrhages. Arch Ophthalmol 115(10):1257–1262

Ravindran RD et al (2011a) Inverse association of vitamin C with cataract in older people in India. Ophthalmology 118(10):1958–1965

Ravindran RD, Vashist P, Gupta SK, Young I, Maraini G et al (2011b) Prevalence and risk factors for vitamin C deficiency in north and south India: a two centre population based study in people aged 60 years and over. PLoS One 6(12):e28588

Ritter LL et al (1993) Alcohol use and lens opacities in the Beaver Dam Eye Study. Arch Ophthalmol 111(1): 113–117

Rotchford AP et al (2003) Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. Ophthalmology 110(2):376–382

Rothman KJ, Greenland S (1998) Modern epidemiology, 2nd edn. Lippincott-Raven, Philadelphia

Rudnicka AR et al (2012) Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology 119(3):571–580

Sanfilippo PG et al (2010) The heritability of ocular traits. Surv Ophthalmol 55(6):561–583

Sapkota YD et al (2010) The prevalence of blindness and cataract surgery in Rautahat District, Nepal. Ophthalmic Epidemiol 17(2):82–89

Sasaki K, Kojima M (1994) Population based cataract epidemiological surveys utilising a photo documentation system. Doc Ophthalmol 88(3–4):277–283

Seddon JM et al (1994) Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case–control Study Group. JAMA 272(18):1413–1420

Seddon JM, George S, Rosner B (2006) Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. Arch Ophthalmol 124(7):995–1001

Shiels A, Bennett TM, Hejtmancik JF (2010) Cat-Map: putting cataract on the map. Mol Vis 16:2007–2015

Shimmyo M et al (2003) Intraocular pressure, Goldmann applanation tension, corneal thickness, and corneal curvature in Caucasians, Asians, Hispanics, and African Americans. Am J Ophthalmol 136(4):603–613

Sia DI et al (2010) Prevalence of and risk factors for primary open-angle glaucoma in central Sri Lanka: the Kandy eye study. Ophthalmic Epidemiol 17(4): 211–216

Skenduli-Bala E et al (2005) Causes of incident visual field loss in a general elderly population: the Rotterdam study. Arch Ophthalmol 123(2):233–238

Smith BT, Belani S, Ho AC (2005) Light energy, cataract surgery, and progression of age-related macular degeneration. Curr Opin Ophthalmol 16(3):166–169

Sommer A et al (1991) Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 109(8):1090–1095

Song W et al (2011) Prevalence of glaucoma in a rural northern china adult population: a population-based survey in Kailu County, Inner Mongolia. Ophthalmology 118(10):1982–1988

Spanish Eyes Epidemiological (SEE) Study Group (SEESG) (2011) Prevalence of age-related macular degeneration in Spain. Br J Ophthalmol 95:931–936

Sparrow JM et al (1986) The oxford clinical cataract classification and grading system. Int Ophthalmol 9(4):207–225

Sperduto RD et al (1993) The Linxian cataract studies. Two nutrition intervention trials. Arch Ophthalmol 111(9):1246–1253

Straub W (1969) Altersbedingte Maculadegeneration (age-related macular degeneration). Deutsche Mediz Wochenschr 26:1385–1386

Sun J, Zhou X, Kang Y, Yan L et al (2012) Prevalence and risk factors for primary open-angle glaucoma in a rural northeast China population: a population-based survey in Bin County, Harbin. Eye 26:283–291

Sunness JS et al (1985) Peripheral retinal function in age-related macular degeneration. Arch Ophthalmol 103(6):811–816

Tamakoshi A et al (1997) Smoking and neovascular form of age related macular degeneration in late middle aged males: findings from a case–control study in Japan. Research Committee on Chorioretinal Degenerations. Br J Ophthalmol 81(10):901–904

Tan JS et al (2007) Statins and the long-term risk of incident age-related macular degeneration: the Blue Mountains Eye Study. Am J Ophthalmol 143(4):685–687

Tan JS et al (2008a) Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 115(2):334–341

Tan JS et al (2008b) Smoking and the long-term incidence of cataract: the Blue Mountains Eye Study. Ophthalmic Epidemiol 15(3):155–161

Tan JS et al (2009) Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol 127(5):656–665

Tarkkanen A, Reunanen A, Kivela T (2008) Frequency of systemic vascular diseases in patients with primary open-angle glaucoma and exfoliation glaucoma. Acta Ophthalmol 86(6):598–602

Tasman W, Jaeger AE (1999) Duane's clinical ophthalmology, vol 1. Lippincott Williams & Wilkins, Philadelphia, chapters 71A, 73, 74

Taylor HR et al (1992) The long-term effects of visible light on the eye. Arch Ophthalmol 110(1):99–104

The Eye Disease Case-Control Study Group (EDCCSG) (1992) Risk factors for neovascular age-related macular degeneration. Arch Ophthalmol 110(12): 1701–1708

The Italian-American Cataract Study Group (1991) Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. Am J Epidemiol 133: 541–553

Tielsch JM et al (1991) Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA 266(3):369–374

Tielsch JM et al (1995) Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. Ophthalmology 102(1):48–53

Tomany SC et al (2004) Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. Ophthalmology 111(7):1280–1287

van der Schaft TL et al (1994) Increased prevalence of disciform macular degeneration after cataract extraction with implantation of an intraocular lens. Br J Ophthalmol 78(6):441–445

van Leeuwen R, Vingerling JR, de Jong PT (2001) Risk of macular degeneration with statin use should be interpreted with caution. BMJ 323(7324):1308

van Leeuwen R et al (2003a) Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. Invest Ophthalmol Vis Sci 44(9):3771–3777

van Leeuwen R et al (2003b) The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study. Arch Ophthalmol 121(4): 519–526

van Leeuwen R et al (2005) Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 294(24):3101–3107

Vandenbroucke JP et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 4(10):e297

VandenLangenberg GM et al (1998) Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 148(2):204–214

Vashist P et al (2011) Prevalence of cataract in an older population in India: the India study of age-related eye disease. Ophthalmology 118(2):272–278

Vijaya L et al (2008) Prevalence of primary open-angle glaucoma in an urban south Indian population and comparison with a rural population. The Chennai Glaucoma Study. Ophthalmology 115(4):648–654

Vinding T et al (1992) Risk factor analysis for atrophic and exudative age-related macular degeneration. An epidemiological study of 1000 aged individuals. Acta Ophthalmol (Copenh) 70(1):66–72

Vingerling JR et al (1995) Macular degeneration and early menopause: a case–control study. BMJ 310(6994): 1570–1571

Wang JJ, Mitchell P, Smith W (1998) Refractive error and age-related maculopathy: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 39(11):2167–2171

Wang JJ et al (2004) Refractive status and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. Clin Experiment Ophthalmol 32(3):255–258

Wang S, Wang JJ, Wong TY (2008) Alcohol and eye diseases. Surv Ophthalmol 53(5):512–525

Wang JJ et al (2009) Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. Am J Epidemiol 169(5):633–641

Wang X et al (2010a) Using the Utah Population Database to assess familial risk of primary open angle glaucoma. Vision Res 50(23):2391–2395

Wang YX et al (2010b) Prevalence of glaucoma in North China: the Beijing Eye Study. Am J Ophthalmol 150(6):917–924

Wang D et al (2011) Intraocular pressure, central corneal thickness, and glaucoma in Chinese adults: the Liwan eye study. Am J Ophthalmol 152(3):454–462

Waudby CJ et al (2011) Cataract research using electronic health records. BMC Ophthalmol 11:32

Weiner DE et al (2011) Kidney function, albuminuria and age-related macular degeneration in NHANES III. Nephrol Dial Transplant 26(10):3159–3165

West SK, Taylor HR (1986) The detection and grading of cataract: an epidemiologic perspective. Surv Ophthalmol 31(3):175–184

West SK, Valmadrid CT (1995) Epidemiology of risk factors for age-related cataract. Surv Ophthalmol 39(4):323–334

West S et al (1989a) Cigarette smoking and risk of nuclear cataracts. Arch Ophthalmol 107(8):1166–1169

West SK et al (1989b) Exposure to sunlight and other risk factors for age-related macular degeneration. Arch Ophthalmol 107(6):875–879

West SK et al (1998) Sunlight exposure and risk of lens opacities in a population-based study: the Salisbury Eye Evaluation project. JAMA 280(8):714–718

Wieberdink RG et al (2011) Age-related macular degeneration and the risk of stroke: the Rotterdam study. Stroke 42(8):2138–2142

Wolfs RC et al (1997) Distribution of central corneal thickness and its association with intraocular pressure: the Rotterdam Study. Am J Ophthalmol 123(6): 767–772

Wolfs RC et al (1998) Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch Ophthalmol 116(12):1640–1645

Wolfs RC et al (2000) Changing views on open-angle glaucoma: definitions and prevalences – The Rotterdam Study. Invest Ophthalmol Vis Sci 41(11): 3309–3321

Wong TY et al (2002) Refractive errors and 10-year incidence of age-related maculopathy. Invest Ophthalmol Vis Sci 43(9):2869–2873

Wu SY et al (2005) Nine-year refractive changes in the Barbados Eye Studies. Invest Ophthalmol Vis Sci 46(11):4032–4039

Wu R et al (2010) Smoking, socioeconomic factors, and age-related cataract: The Singapore Malay Eye study. Arch Ophthalmol 128(8):1029–1035

Xu L, You QS, Jonas JB (2009) Prevalence of alcohol consumption and risk of ocular diseases in a general population: the Beijing Eye Study. Ophthalmology 116(10):1872–1879

Xu L, Wang YX, Jonas JB (2010) Level of education associated with ophthalmic diseases. The Beijing Eye Study. Graefes Arch Clin Exp Ophthalmol 248(1):49–57

Yanagi M et al (2011) Vascular risk factors in glaucoma: a review. Clin Experiment Ophthalmol 39(3): 252–258

Yang K et al (2011) Prevalence of age-related macular degeneration in a rural Chinese population: the Handan Eye Study. Ophthalmology 118(7):1395–1401

Yasuda M et al (2009) Nine-year incidence and risk factors for age-related macular degeneration in a defined Japanese population the Hisayama study. Ophthalmology 116(11):2135–2140

Yip JL et al (2007) Socioeconomic status, systolic blood pressure and intraocular pressure: the Tanjong Pagar Study. Br J Ophthalmol 91(1):56–61

Younan C et al (2003) Cardiovascular disease, vascular risk factors and the incidence of cataract and cataract surgery: the Blue Mountains Eye Study. Ophthalmic Epidemiol 10(4):227–240

# 5 Age-Related Macular Degeneration and Primary Open-Angle Glaucoma: Genetics and Gene-Environment Interaction

Gabriëlle H.S. Buitendijk, Henriët Springelkamp, Lintje Ho, and Caroline C.W. Klaver

## 5.1 Introduction

The genetics of AMD as well as of POAG have been exciting research areas during the last decade. The advances in molecular genetic techniques paved the way for great progress in the discovery of genes and led to the identification of many disease-associated risk variants. In this chapter, we will focus on the genes which have good evidence to be involved in the pathogenesis of either of these disorders.

## 5.2 Age-Related Macular Degeneration (AMD)

### 5.2.1 Genetic Factors

Although familial occurrence had been known for many years, major advances in the identification of genetic factors for AMD were achieved after the start of Genome Wide Association Studies (GWAS). We will discuss the currently known AMD-associated genes and their importance to the disease. A summary of the genes can be found in Table 5.1.

Gabriëlle H.S. Buitendijk and Henriët Springelkamp have contributed equally to this chapter

G.H.S. Buitendijk (✉) • H. Springelkamp • L. Ho
C.C.W. Klaver
Department of Ophthalmology and Epidemiology,
Erasmus Medical Center,
Rotterdam, The Netherlands
e-mail: g.buitendijk@erasmusmc.nl

### 5.2.2 The Complement Pathway Genes

#### 5.2.2.1 Complement Factor H (*CFH*)

*CFH* is one of the two major AMD genes. The CFH protein is a key regulator of the complement pathway – it inhibits the activation of complement component C3 to C3b and degrades C3b, thereby limiting the amplification phase of the alternative complement cascade (Rodriguez de Cordoba et al. 2004). CFH is present in serum, not membrane-bound, expressed in the retinal pigment epithelium, and can be found in drusen (Johnson et al. 2001; Hageman et al. 2005).

First reports on an association between *CFH* and AMD stem from 2005 (Klein et al. 2005; Haines et al. 2005; Edwards et al. 2005), and since then, this finding has been replicated by numerous studies in different populations (Rivera et al. 2005; Souied et al. 2005; Zareparsi et al. 2005; Baird et al. 2006a; Chen et al. 2006; Conley et al. 2006; Despriet et al. 2006; Fuse et al. 2006; Lau et al. 2006; Magnusson et al. 2006; Schaumberg et al. 2006; Seddon et al. 2006; Seitsonen et al. 2006; Sepp et al. 2006; Brantley et al. 2007; DeAngelis et al. 2007; Fisher et al. 2007; Mori et al. 2007; Pulido et al. 2007; Tedeschi-Blok et al. 2007; Weger et al. 2007; Wegscheider et al. 2007; Chowers et al. 2008a; Chu et al. 2008; Droz et al. 2008; Kim et al. 2008; Ng et al. 2008; Xu et al. 2008; Ziskind et al. 2008; Ricci et al. 2009; Cui et al. 2010; Gao et al. 2010; Liu et al. 2010; Losonczy et al. 2011). The well-known risk allele Y402H is common in Caucasians and Africans (~36 %) but much less so

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_5, © Springer-Verlag Berlin Heidelberg 2013

**Table 5.1** Overview of major genes associated with AMD

| Gene | Chrom[a] | Variant | Effect allele | EAF | OR (95 %CI) het[b] | OR (95 % CI) hom[c] | Function | References, meta-analyses |
|---|---|---|---|---|---|---|---|---|
| *CFH* | 1 | rs10661170 (Y402H) | C | 0.349 | 2.50 (1.96–3.30) | 6.32 (4.25–9.48) | Key regulator of the alternative complement pathway and inhibits C3 activation | Thakkinstian et al. (2006) |
| *C3* | 19 | rs22330199 (R102G) | G | 0.193 | 1.44(1.33–1.56) | 1.88 (1.59–2.23) | Activation of C3 is crucial for the formation of membrane attack complexes that leads to cell lysis | Thakkinstian et al. (2011) |
| | | rs1047286 (P314L) | A | 0.196 | 1.27(1.15–1.41) | 1.70 (1.27–2.11) | | |
| *CFI* | 4 | rs10033900 | C | Controls: 0.39 | 0.99 (0.61–1.62) | 0.28 (0.11–0.69) | CFI is regulated by CFH and functions as a cofactor for the cleavage and inactivation of C3b | Kondo et al. (2010) |
| *ARMS2* | 10 | rs10490429 (A69S) | T | Controls: 0.25 | 2.35 (2.07–2.67) | 7.51 (5.71–9.66) | ARMS2 may be involved in mitochondrial function in the retinal pigment epithelium cells | Tang et al. (2009) |
| *HTRA1* | | rs11200638 | A | Controls: 0.32 | 2.33 (2.01–2.71) | 9.26 (7.27–11.91) | HTRA1 may inhibit signaling of TGF-b proteins | |

| Gene | Chrom[a] | Variant | Effect allele | EAF[d] | OR (95 % CI)[e] | Function | References |
|---|---|---|---|---|---|---|---|
| *C2/CB* | 6 | rs641153 (R32Q) | A | Controls: 0.10 | 0.29 (0.17–0.48) | C2 and CB are activators of the alternative and classical pathway | Spencer et al. (2007) |
| *APOE* | 19 | ε4 | – | Controls: ~0.16 | 0.54 (0.41–0.70) | APOE is a key regulator of lipid and cholesterol transport in the central nervous system | Schmidt et al. (2002) |
| *TIMP3* | 22 | rs9621532 | A | Controls: 0.95 | 1.41 (1.27–1.57) | TIMP3 is involved in degradation of the extracellular matrix in the retina | Chen et al. (2010) |
| *LIPC* | 15 | rs493258 | C | Controls: 0.56 | 1.14 (1.09–1.20) | LIPC is involved in mediating the uptake of HDL-c at the cell surface | Chen et al. (2010) |
| | | rs10468017 | T | Controls: 0.30 | 0.82 (0.77–0.88) | | Neale et al. (2010) |
| *CETP* | 16 | rs3764261 | A | Controls: 0.32 | 1.19 (1.12–1.27) | CETP plays an important role in the production and degradation of HDL-c | Chen et al. (2010) |
| *COL8A1* | 3 | rs13095226 | C | 0.12 | 1.24 (1.13–1.35) | Collagen type VIII is a major component of Bruch's membrane and the choroidal stroma | Neale et al. (2010) |
| *COL10A1* | 6 | rs1999930 | T | Controls: 0.30 | 0.87 (0.83–0.91) | Collagen type X is expressed by hypertrophic chondrocytes | Yu et al. (2011b) |
| *VEGFA* | 6 | rs4711751 | T | Controls: 0.30 | 1.15 (1.10–1.21) | VEGFA increases vascular permeability, angiogenesis, cell growth, and migration of endothelial cells | Yu et al. (2011b) |

[a]Chrom = Chromosome
[b]OR het = Odd's ratio for heterozygotes, carriers of one risk allele
[c]OR hom = Odd's ratio for homozygotes, carriers of two risk alleles
[d]EAF = Effect allele frequency
[e]OR = Odd's ratio

in Asians (~7–15 %) and Hispanics (~17 %) (Nonyane et al. 2010). Functionally, this and other risk alleles have been shown to alter CFH binding, thereby impairing the regulatory function of CFH, increasing complement activation, and subsequently causing an inflammatory response and cell death (Johnson et al. 2006; Laine et al. 2007; Skerka et al. 2007; Edwards et al. 2005; Hageman et al. 2005; Haines et al. 2005; Klein et al. 2005; Despriet et al. 2006).

*CFH* is located in a large region of linkage disequilibrium. Apart from Y402H, many other variants have been shown to be associated with increased risk of AMD. A noncoding variant (rs1410996) was found to have an even stronger association than Y402H (Li et al. 2006b; Maller et al. 2006). In particular in Asian populations, the Y402H variant was not significantly associated with AMD, whereas other variants including rs1410996 were (Mori et al. 2007; Cui et al. 2010). The genes in the vicinity of *CFH*, such as *CFHR1-5*, have gene functions similar to *CFH* and have also been associated with AMD. A haplotype carrying a deletion of *CFHR1* and *CFHR3* (delCFHR1/3) was reported to have a protective effect and occurred in 20 % of controls and 8 % of cases (Hughes et al. 2006; Spencer et al. 2008a). The proteins encoded by these genes are absent in serum of persons who are homozygous for delCFHR1/3 (Hughes et al. 2006). *CFHR1* and *CFHR3* contain a C3-binding site and deletion of these genes may reduce competition for the binding of CFH to C3b, enhancing inhibitory activity by CFH. DelCFHR1/3 was more frequent in African Americans (16 %) and less common in Hispanics (6.8 %) and European Americans (4.7 %) (Cann et al. 2002).

#### 5.2.2.2 Complement Factor B (*CFB*)/ Complement Component 2 (*C2*)

Complement factor B (CFB) and complement component 2 (C2) are activators of the alternative and classical pathways, respectively. Four variants in the *CFB* and *C2* gene located on chromosome 6p21 have been shown to have a strong protective effect: *CFB* R32Q, which is in nearly complete linkage disequilibrium with *C2* IVS10, and *CFB* L9H, which is in nearly complete linkage disequilibrium with *C2* E318D (Gold et al. 2006; Maller et al. 2006; Spencer et al. 2007; Jakobsdottir et al. 2008; Francis et al. 2009; McKay et al. 2009; Richardson et al. 2009; Kaur et al. 2010).

Genetic and functional data suggest that *CFB* variants rather than *C2* variants are likely to have caused the observed protection. Only the *CFB* R32Q variant results in inferior C3b-binding affinity, leading to a lower potential to amplify complement activation (Lokki and Koskimies 1991; Montes et al. 2009). Moreover, the majority of proteins of the alternative pathway (e.g., CFH, CFB) are present in drusen, whereas proteins from the classical pathway (e.g., C2) are not (Mullins et al. 2000; Crabb et al. 2002). Good epidemiologic analysis with adjustment for confounders showed that the association with *C2* R32Q was robust (OR, 0.21; 95 % CI, 0.11–0.39), while the association with *C2* E318D became insignificant (OR, 0.60; 95 % CI, 0.25–1.47) (Spencer et al. 2007). These data suggest that the *C2* variants show residual association with AMD originating from their high linkage disequilibrium with *CFB*.

#### 5.2.2.3 Complement Component 3 (*C3*)

Complement component C3 is the convergence point of all complement pathways (classical, lectin, and alternative). Activation of C3 is crucial for the formation of membrane attack complexes that leads to cell lysis (Janssen et al. 2006). The *C3* gene is located on chromosome 19p13.3–13.2. The amino acid changes caused by the *C3* variants R102G and P314L may alter the binding capacity of C3 to pathogenic cell surfaces or other complement proteins (Sahu and Lambris 2001; Janssen et al. 2006; Nishida et al. 2006). A causal relation with AMD is plausible, since C3 mRNA is present in neural retina, choroids, and retinal pigment epithelium (Mullins et al. 2000); its cleavage product C3a is present in drusen (Hageman et al. 2001; Johnson et al. 2001), and C3a can induce vascular endothelial growth factor expression and promote choroidal neovascularization (Nozaki et al. 2006).

The two functional variants, R102G (rs2230199) and P314L (rs1047286), are in high

linkage disequilibrium. They have both been identified as genetic risk factors for AMD (Maller et al. 2007; Yates et al. 2007; Edwards et al. 2008; Spencer et al. 2008b; Despriet et al. 2009; Park et al. 2009; Scholl et al. 2009; McKay et al. 2010; Thakkinstian et al. 2011). R102G has also been implicated in the progression from the earlier stages of AMD to late AMD (Francis et al. 2009). The two initial investigations as well as later studies concluded that R102G is more significant in AMD causality than P314L (Yates et al. 2007; Spencer et al. 2008b; Maller et al. 2007; Bergeron-Sawitzke et al. 2009; Despriet et al. 2009; Thakkinstian et al. 2011; Bergeron-Sawitzke et al. 2009; Despriet et al. 2009; Park et al. 2009).

An allele-dose effect for R102G was observed in the various Caucasian studies with an increased risk of 1.4–1.7 for heterozygotes and 1.8–3.3 for homozygotes. The Rotterdam Study (RS) found associations of the *C3* variants with early as well as late AMD and reported that the risk increase was most prominent for the mixed type of AMD (both geographic atrophy and neovascular AMD present) (Despriet et al. 2009). The effect of the *C3* alleles is independent from *CFH* Y402H and *ARMS2* A69S (Despriet et al. 2009; Park et al. 2009).

#### 5.2.2.4 Complement Factor I (*CFI*)

The CFI protein is regulated by CFH and functions as a cofactor for the cleavage and inactivation of C3b. Recently, several variants near the *CFI* gene have been associated with risk of AMD in Caucasian as well as Asian populations (Wang et al. 2008b; Fagerness et al. 2009; Chen et al. 2010; Ennis et al. 2010; Kondo et al. 2010; Peter et al. 2011). In a Japanese study, rs10033900 had a protective effect with OR 0.28 (95 % CI, 0.11–0.69) for homozygous carriers of the minor allele. No association was found for heterozygous carriers (OR, 0.99; 95 % CI, 0.61–1.62). A recent genome-wide association study found that the major allele of rs2285714 was associated with an increased risk of 1.31 (95 % CI, 1.18–1.45). Ennis et al. reported significantly ($P<0.05$) protective effects for rs11728699, rs6854876, rs7439493, and rs13117504 with ORs ranging from 0.68 to 0.74 ($P<0.05$), and these SNPs also tagged significant protective (GCAG, OR 0.69) and causative (TGGC, OR 1.34) haplotypes (Ennis et al. 2010; Fagerness et al. 2009).

#### 5.2.2.5 The *ARMS2-HTRA1* (10q26) Locus

Linkage studies had already identified a susceptibility locus at chromosome 10q26. GWA studies conformed this locus as the second major contributor to the pathogenesis of AMD (Majewski et al. 2003; Seddon et al. 2003, 2007; Iyengar et al. 2004; Kenealy et al. 2004; Weeks et al. 2004; Fisher et al. 2005; Jakobsdottir et al. 2005; Rivera et al. 2005; Schmidt et al. 2006; Yang et al. 2006; Dewan et al. 2006; Despriet et al. 2007; Hughes et al. 2007; Kanda et al. 2007; DeAngelis et al. 2008; Fritsche et al. 2008; Gibbs et al. 2008; Richardson et al. 2010; Wang et al. 2010a; Yang et al. 2010). As this region contains many genes in high linkage disequilibrium (*Pleckstrin homology domain-containing protein family A member 1* (*PLEKHA1*), *LOC387715* (or *age-related maculopathy susceptibility gene 2*, *ARMS2*), and *high-temperature requirement factor A1* (*HTRA1*) gene), controversy exists about which gene is the AMD susceptibility gene.

In the *ARMS2* gene, rs10490924 has repeatedly been reported to increase risk of AMD up to 15 times (Fisher et al. 2005; Jakobsdottir et al. 2005; Rivera et al. 2005; Schmidt et al. 2006; Despriet et al. 2007; Hughes et al. 2007; Kanda et al. 2007; Seddon et al. 2007; Fritsche et al. 2008; Yang et al. 2010; Wang et al. 2010a). This functional SNP causes an A69S change and has been described as the causal SNP that by itself could explain the bulk of the association between the 10q26 region and AMD (Kanda et al. 2007). The precise function of *ARMS2* in AMD remains to be elucidated. Disorganized mitochondrial membranes, as well as decreased number of mitochondria in retinal pigment epithelium cells of AMD donors, have provided evidence of mitochondrial dysfunction in AMD (Barron et al. 2001; Feher et al. 2006). This suggests that *ARMS2* may jeopardize mitochondrial function and consequently lead to the formation of reactive oxygen species, apoptosis, and AMD (Barron et al. 2001; Liang and Godley 2003; Feher et al. 2006; Fritsche et al. 2008; Jarrett et al. 2008;

Wang et al. 2008a). Moreover, immunohistochemical studies located the ARMS2 protein to the mitochondrial outer membrane, in particular of rods and cones (Kanda et al. 2007; Fritsche et al. 2008). However, its presence has also been reported in the cellular cytosol (Wang et al. 2009a) and the extracellular matrix (Kortvely et al. 2010).

Meta-analyses of the *HTRA1* gene reported an increased risk of AMD for homozygous (OR, 9.26; 95 % CI, 7.27–11.91) as well as heterozygous (OR, 2.33; 95 % CI, 2.01–2.71) carriers of the rs11200638 risk allele (Tong et al. 2010). Stratified analyses revealed that rs11200638 was significantly associated with choroidal neovascularization (CNV) but not with geographic atrophy (GA) and that the causative effect was stronger in Caucasians than in Asians (Chen et al. 2009; Tang et al. 2009). Also for this gene, various lines of evidence support involvement in AMD. The rs11200638 risk allele has been associated with higher levels of *HTRA1* mRNA and protein in some studies (Yang et al. 2006, 2010; Chan et al. 2007; Tuo et al. 2008), although two other studies with larger datasets could not validate this finding in heterologous expression systems (Kanda et al. 2007; Chowers et al. 2008b). Furthermore, HTRA1 may inhibit signaling of TGF-ß proteins, which have been reported to act as negative growth regulators in the retina and RPE (Zumbrunn and Trueb 1996; Mathura et al. 2000; Oka et al. 2004). In addition, *HTRA1* may stimulate the degradation of extracellular matrix through enhanced expression of matrix metalloproteases. Consequently, overexpression of *HTRA1* may affect the integrity of Bruch's membrane and RPE contributing to AMD development. Recently, Richardson et al. (2010) found rs3793917 (located between *ARMS2* and *HTRA1*) to be most associated with AMD (OR, 3.45; 95 % CI, 2.36–5.05) and indicated that the intergenic region between this SNP and *HTRA1* rs11200638 was most likely to confer AMD risk. However, they could not distinguish rs3793917 from rs11200638 and rs10490924 to explain causality since they were all in high linkage disequilibrium.

Common haplotypes encompassing both the *ARMS2* and the *HTRA1* genes have also been linked to AMD. Gibbs et al. (2008) described a common haplotype TAT tagged by rs10490924, rs11200638, and rs2293870 that significantly predisposed to AMD ($P = 2.70 \times 10^{-9}$) and a haplotype GGG that was significantly protective against AMD ($P = 0.003$). Yang et al. (2010) also found a haplotype T-G-Wt-G tagged by rs2736911, rs10490924, in/del/Wt, and rs11200638, which was protective in Caucasian as well as Chinese populations ($P < 0.007$). They also observed that the in/del or the rs11200638 risk allele by itself was insufficient to alter *HTRA1* expression and found that a common disease haplotype including both the in/del and rs11200638 leads to upregulation of *HTRA1* (Yang et al. 2010). Hence, they proposed a binary model where downregulation of *ARMS2* and concomitant upregulation of *HTRA1* best explained the risk associated with the 10q26 locus. Further functional analyses in larger datasets are warranted to conclude what the key genetic contributors in the 10q26 locus are.

### 5.2.3 The Lipid-Related Genes

#### 5.2.3.1 Apolipoprotein E (*APOE*)

Apolipoprotein E is a key regulator of lipid and cholesterol transport in the central nervous system (Mahley 1988) and has been linked to various neurodegenerative and cardiovascular diseases (e.g., Alzheimer's disease and stroke) (Evans et al. 1997; Slooter et al. 1997; Ishida et al. 2004). In the eye, *APOE* is expressed in photoreceptor cells, retinal ganglion cells, Müller cells, retinal pigment epithelium, Bruch's membrane, choroid, and in the disease-associated lesions: drusen and basal laminar deposits (Klaver et al. 1998; Mullins et al. 2000; Anderson et al. 2001, 2004; Crabb et al. 2002; Li et al. 2006a; Wang et al. 2010b). There are three common allelic variants of the *APOE* gene: ε2, ε3, and ε4, with ε3 being the most prevalent (Zannis 1986; Jarvik 1997). The majority of studies support a protective effect of the *APOE* ε4 allele against AMD (Klaver et al. 1998; Souied et al. 1998; Pang et al. 2000; Schmidt et al. 2000, 2002; Simonelli et al. 2001; Schultz et al. 2003; Baird et al. 2004; Gotoh et al. 2004;

Zareparsi et al. 2004; Baird et al. 2006b; Bojanowski et al. 2006; Wong et al. 2006; Utheim et al. 2008), though in some reports, this inverse association failed to reach statistical significance (Pang et al. 2000; Schultz et al. 2003; Gotoh et al. 2004; Wong et al. 2006; Utheim et al. 2008). Stratification of late AMD into GA and CNV showed that the greatest protective effect for the ε3ε4 genotype was in individuals with GA (OR 0.35, 95 % CI 0.13–0.92) (Baird et al. 2004). The *APOE* ε2 allele has mainly been associated with a nonsignificant but increased risk of AMD (Klaver et al. 1998; Souied et al. 1998; Simonelli et al. 2001; Schmidt et al. 2002; Schultz et al. 2003; Baird et al. 2004; Zareparsi et al. 2004; Wong et al. 2006; Tikellis et al. 2007).

Several studies reported that ε4 carriers have significantly lower CRP levels than noncarriers, especially compared to ε2 carriers. CRP level reportedly decreases in a dose-dependent order of ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4 (Manttari et al. 2001; Austin et al. 2004; Judson et al. 2004; Marz et al. 2004; Eiriksdottir et al. 2006; Rontu et al. 2006). In addition, *APOE* ε2 appears to enhance expression by RPE cells of the vascular endothelial growth factor and fibroblast growth factor (Lee et al. 2007), whereas their expression is reportedly suppressed by *APOE* ε4 (Malek et al. 2005; Bojanowski et al. 2006). This indicates that *APOE* ε2 induces neovascularization by altering angiogenic cytokines, whereas *APOE* ε4 limits this process. And in contrast to ε2, *APOE* ε4 has positive charges which diminish hydrophobicity of Bruch's membrane and results in better clearance of debris. Moreover, ε4 carriers reportedly have 36 % lower risk of hypertension than noncarriers (Katsuya et al. 2002). Another interesting finding is that APOE ε4 levels seem to decrease with advancing age (Rontu et al. 2006), which may reduce transport of lipids and cell debris, culminating in a higher rate of AMD in older age. APOE also plays an important role in the maintenance of retinal membrane cell: Lipids are released from the degenerating cell membrane, and astrocytes react by synthesizing APOE to bind the free cholesterol and lipids and to distribute them for reuse in cell membrane biosynthesis (Grindle and Marshall 1978; Ignatius et al. 1986; Poirier et al. 1993). Based on the cumulative empirical evidence and pooled data outlined above, it can be proposed that the *APOE* ε4 offers a reduced risk for onset, severity, and progression rate of AMD, in contrast to *APOE* ε2.

#### 5.2.3.2 Hepatic Lipase (*LIPC*)

Two parallel published GWAS reported causative variants for the *LIPC* gene (Chen et al. 2010; Neale et al. 2010). *LIPC* has been associated with high-density lipoprotein cholesterol (HDL-c) levels in blood (Willer et al. 2008; Kathiresan et al. 2009) and is involved in mediating the uptake of HDL-c at the cell surface (Hasham and Pillarisetti 2006). *LIPC* is expressed in the retina and modification of HDL-related efficiency could influence the risk of AMD because HDL is an important transporter of lutein/zeaxanthin (Tserentsoodol et al. 2006; Wang et al. 2007; Neale et al. 2010). The common allele of rs493258 near the *LIPC* gene on chromosome 15q22 (OR, 1.14; 95 % CI, 1.09–1.20; frequency in controls ~0.56; $P = 1.3 \times 10^{-7}$) increased the risk of AMD, whereas the minor allele of rs10468017, a functional promoter variant, (OR, 0.82; 95 % CI, 0.77–0.88; frequency in controls ~0.30; $P = 1.34 \times 10^{-8}$) had a protective effect. However, confirmation of the protective variant was achieved after targeted examination of the suggestive markers of the GWAS performed by Neale et al. (2010).

#### 5.2.3.3 Cholesterylester Transfer Protein (*CETP*)

The rare allele of rs3764261 at the *CETP* gene on chromosome 16q21 (OR, 1.19; 95 % CI, 1.12–1.27; frequency in controls ~0.32; $P = 7.4 \times 10^{-7}$) is associated with an increased risk of AMD (Chen et al. 2010) and has recently been replicated by Yu et al. (2011a). *CETP* plays an important role in the production and degradation of HDL-c and is expressed in the retina (Tserentsoodol et al. 2006; Neale et al. 2010).

#### 5.2.3.4 Lipoprotein Lipase (*LPL*)

Chen et al. (2010) reported also the variant rs12678919 at *LPL* on chromosome 8p22 (OR,

1.38; 95 % CI, 1.11–1.43; $P = 3 \times 10^{-3}$). This variant was not significant but consistent with the hypothesis that HDL metabolism is associated with AMD pathogenesis; *LPL* plays, like *CETP*, an important role in the production and degradation of HDL-c (Tserentsoodol et al. 2006; Neale et al. 2010). Recently, an association, although not significant, between *LPL* rs12678919 and late AMD was suggested by Peter et al. (2011) (OR, 0.5, 95 % CI, 0.2–1.2, $P = 0.10$) for carriers of 1 or 2 G alleles compared to noncarriers. The G allele increases serum HDL levels ($P < 10^{-10}$, 2.44 mg/dl increase per G allele), confirming the role of *LPL* in the HDL metabolism (Willer et al. 2008).

#### 5.2.3.5 ATP-Binding Cassette Subfamily A Member 1 (*ABCA1*)

*ABCA1* is involved in mediating the uptake of HDL-c at the cell surface and has been shown to be expressed in the retina (Hasham and Pillarisetti 2006; Tserentsoodol et al. 2006; Neale et al. 2010). The variant rs1883025 near *ABCA1* on chromosome 9q22 (OR, 1.15; 95 % CI, 1.07–1.23; $P = 5.6 \times 10^{-4}$) has been suggested by Chen et al. (2010) to be associated with AMD. Several other studies confirmed this suggestion and showed a significantly higher risk allele frequency in AMD patients compared with control individuals ($P = 0.00027$) (Neale et al. 2010; Fauser et al. 2011; Yu et al. 2011a, b).

With increasing age, lipids and cholesterol accumulate underneath the RPE and are constituents of drusen (Mullins et al. 2000; Curcio et al. 2005). The HDL-c-associated variants might affect the formation of drusen and subsequently the development of AMD. The "non-risk" TT-genotype of *ABCA1* rs1883025 had a significant protective effect for intermediate and large drusen: (OR, 0.48; 95 % CI; 0.27–0.85), (OR, 0.41; 95 % CI, 0.23–0.74), respectively (Yu et al. 2011b).

### 5.2.4 Collagen-Related Genes

#### 5.2.4.1 Alpha Chain of Type VIII Collagen (*COL8A1*)

The *COL8A1* gene on chromosome 3 encodes for one of the alpha chains of type VIII collagen, a major component of the multiple basement membranes in the eye, including Bruch's membrane and the choroidal stroma (Tamura et al. 1991; Neale et al. 2010). The intronic variant rs13095226 was associated with a slight increased risk of AMD (OR, 1.24; 95 % CI, 1.13–1.35; $P = 2.50 \times 10^{-6}$).

#### 5.2.4.2 Alpha Chain of Type X Collagen (*COL10A1*)

Recently, a GWAS has published a novel loci, rs1999930 near the *COL10A1* gene (OR, 0.87; 95 % CI, 0.83–0.91; $P = 1.1 \times 10^{-10}$). COL10A1 is a short-chain collagen expressed by hypertrophic chondrocytes during endochondral ossification. Although no relation of COL10A1 with the retina has been found, the previous finding of the collagen gene *COL8A1* implicates a role for collagen in a causal pathway for AMD (Yu et al. 2011a).

### 5.2.5 Other Genes

#### 5.2.5.1 Tissue Inhibitor of Metalloproteinases-3 (*TIMP3*)

Candidate gene analyses initially found no evidence of linkage or association between AMD and *TIMP3* on chromosome 22q12.1–13.2 (De La Paz et al. 1997; Felbor et al. 1997). Recently, a GWAS found the region near *TIMP3* to be a susceptibility locus (Chen et al. 2010), which was previously reported by one linkage study (Abecasis et al. 2004). TIMP3 is a metalloproteinase involved in degradation of the extracellular matrix in the retina (Strunnikova et al. 2010) and is mutated in Sorsby's fundus dystrophy (Weber et al. 1994). The common variant, rs9621532, nearby *TIMP3* was associated with increased risk of AMD (OR, 1.41; 95 % CI, 1.27–1.57; frequency in controls ~0.95; $P = 1.1 \times 10^{-11}$).

#### 5.2.5.2 Vascular Endothelial Growth Factor A (*VEGFA*)

VEGFA is a member of the VEGF family and functions to increase vascular permeability, angiogenesis, cell growth, and migration of endothelial cells. VEGFA is also a target in the treatment of CNV with anti-VEGF therapy. Haines et al. (2006) found a strong association

for the variant rs2010963 with linkage analysis (LOD score = 1.32, $P = 0.0001$) in early and late AMD but a moderate result in a later case–control setting ($P = 0.02$). Recently, a new variant near the *VEGFA* gene was published. The variant rs4711751 on 6p12 near *VEGFA* (OR, 1.15; 95 % CI, 1.10–1.21; $P = 8.7 \times 10^{-9}$) was not in LD with the earlier found variant, indicating a novel region associated with AMD. Unfortunately, the variant found by Haines et al. (2006) could not be replicated (Yu et al. 2011a).

#### 5.2.5.3 Tumor Necrosis Factor Receptor Superfamily 10 A (*TNRSF10A*)

*TNRSF10A* encodes for TRAILR1, a TRAIL receptor, which is broadly expressed in human adult RPE (Strunnikova et al. 2010). Arakawa et al. (2011) reported a variant, rs13278062 near *TNRSF10A* on chromosome 8p21 (OR, 0.73; 95 % 0.67–0.80; $P = 1.03 \times 10^{-12}$) to be associated with exudative AMD in a Japanese population.

### 5.2.6 Gene-Gene and Gene-Environment Interactions

#### 5.2.6.1 *CFH* Y402H

The RS reported interaction between *CFH* Y402H and smoking, C-reactive protein level, and erythrocyte sedimentation rate (ESR) (Despriet et al. 2006), meaning that the joint effect of each determinant with Y402H was significantly greater than the sum of the independent effects. Compared to persons with the homozygous non-risk (TT) genotype and normal ESR levels, persons with the homozygous risk (CC) genotype and elevated ESR levels had a risk of 20.2 (95 % CI, 9.5–43.0) for late AMD. Higher serum CRP levels in persons with the CC-genotype augmented AMD risk to 27.7 (95 % CI, 10.7–72.0) compared to persons with the lowest CRP levels and the TT-genotype.

Current smokers with the CC-genotype had an OR of 34.0 (95 % CI, 13.0–88.6) for late AMD relative to individuals with the TT-genotype who never smoked. Other studies also observed stronger effects of *CFH* Y402H among smokers (Seddon et al. 2006; Sepp et al. 2006; DeAngelis et al. 2007; Schaumberg et al. 2007; Scott et al. 2007; Delcourt et al. 2011). DeAngelis et al. (2007) further specified that smoking ten pack-years or more and having the CC-genotype was estimated to increase risk of CNV 144-fold compared with smoking less than ten pack-years and having the CT- or TT-genotype.

AREDS reported a significant interaction between *CFH* Y402H and BMI (Seddon et al. 2006). Higher BMI (≥25) did not increase the risk of AMD for persons with the TT-genotype (OR 0.7; 95 % CI 0.4–1.2), whereas it did increase risk for those with the CT- (OR 2.2; 95 % CI 1.3–4.0) and CC-genotype (OR 5.9; 95 % CI 3.1–11.4).

Gold et al. reported that the protection conferred by *C2* and/or *CFB* was strongest in persons with the *CFH* CC-genotype (OR = 0.27), intermediate in persons with the CT-genotype (OR = 0.36), and weakest in persons with the TT-genotype (OR = 0.44). However, the confidence intervals of all these estimates overlapped (Gold et al. 2006).

Two studies have examined interaction between genetic variants and antioxidants in the development of late AMD. AREDS calculated the risk of progression to late AMD for the CFH Y402H and *ARMS2* A69S genotypes in various antioxidant treatment arms. A high zinc dosage was most protective against AMD in persons with the homozygous non-risk *CFH* genotype but produced the greatest, albeit nonsignificant, protection in persons carrying the risk variant of *ARMS2* (Klein et al. 2008). The blue mountain eye study (BMES) found that high fish intake resulted in greater protection against late AMD in homozygous carriers of Y402H than in noncarriers (Wang et al. 2009b). In addition, the RS showed that higher dietary intake of zinc, w-3 fatty acids, b-carotene, and lutein/zeaxanthin can attenuate the incidence of early AMD in those carrying these genetic risk variants (Ho et al. 2011) (Fig. 5.1).

#### 5.2.6.2 *ARMS2-HTRA1*

Although not all studies reported statistical interaction, the majority supported a strong combined effect of smoking and *ARMS2* A69S in AMD susceptibility (Weeks et al. 2004; Schmidt et al. 2006; Francis et al. 2007; Ross et al. 2007; Schaumberg et al. 2007; Neuner et al. 2008; Seitsonen et al. 2008; Wang et al. 2008c; Lee et al. 2010). Interaction analyses by Schmidt et al. between

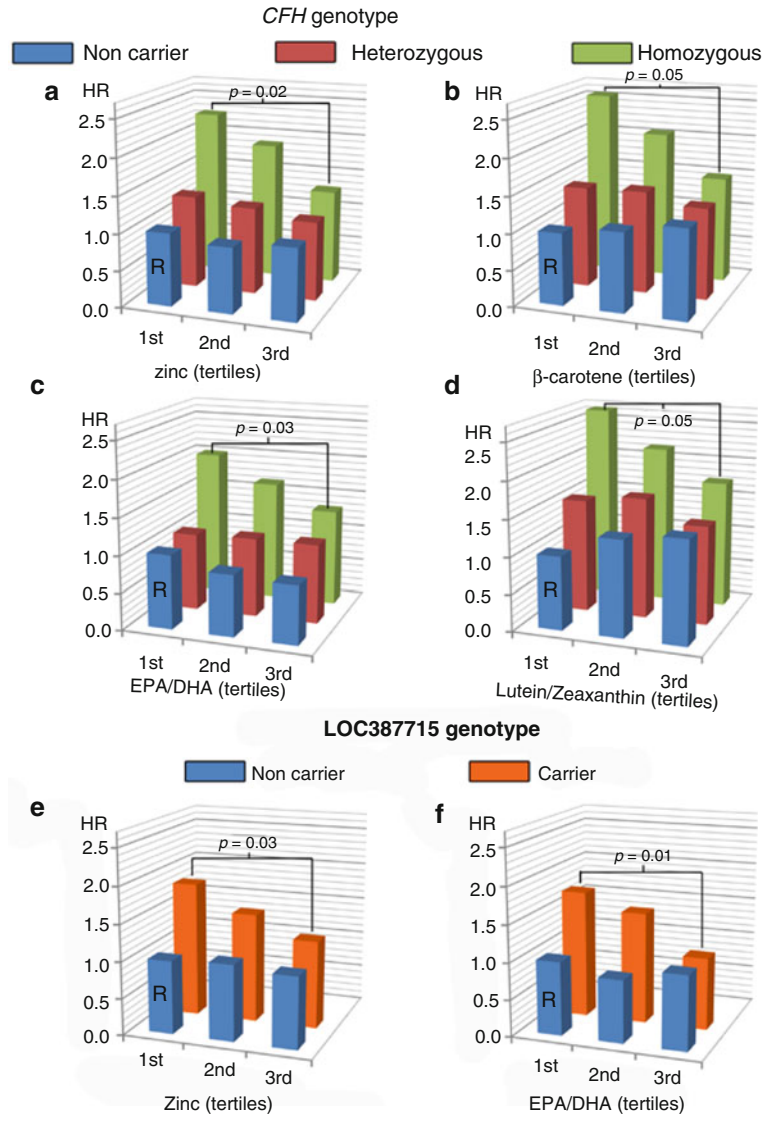


**Fig. 5.1** (**a**–**d**) Joint effect of dietary nutrient intake and *CFH* Y402H genotype on the risk of Early AMD. (**e**–**f**) Joint effect of dietary nutrient intake and *LOC387715* (*ARMS2*) A69S genotype on the risk of Early AMD. R is the common reference group. †HRs are estimates of the relative risk of early AMD and represent the risk of disease (early AMD vs. no AMD) in the various genetic-environmental risk groups divided by the risk of disease (early AMD vs. no AMD) in the common reference group (noncarriers – first tertile of nutrient intake). HRs are estimated with Cox regression analyses and included age, sex, smoking status, and atherosclerosis

number of pack-years of smoking and A69S genotypes revealed that in affected persons, the frequency of the homozygous risk (TT) genotype linearly increased with increasing pack-years irrespective of age and gender, with a corresponding decrease in the homozygous non-risk (GG) genotype frequencies ($P<0.05$) (Schmidt et al. 2006). When comparing current smokers to never smokers, risks for heterozygotes (GT) increased three- to six-fold, while for the homozygotes (GG), risk increased 10- to 27-fold (Francis et al. 2007; Schaumberg et al. 2007).

Combined effects on the likelihood of early or late AMD were demonstrated by the BMES for the A69S GT- and TT-genotypes with the marker's high-sensitivity CRP (ORs, 1.2 for the highest tertile alone, 1.6 for GT- and TT-genotypes alone, and 2.2 for both GT- and TT-genotypes plus the highest tertile, compared with the GG-genotype with the two lower tertiles), IL-6 (corresponding ORs, 1.1, 1.6, and 2.2), sICAM-1 (ORs, 1.0, 1.5, and 2.3, respectively), and PAI-1 (ORs, 1.3, 1.7, and 2.3, respectively), but not with WCC, fibrinogen, homocysteine, and von Willebrand factor (Wang et al. 2008c).

Interaction with antioxidants and *ARMS2* was studied within the same settings as *CFH* and resulted in similar effects (Fig. 5.1).

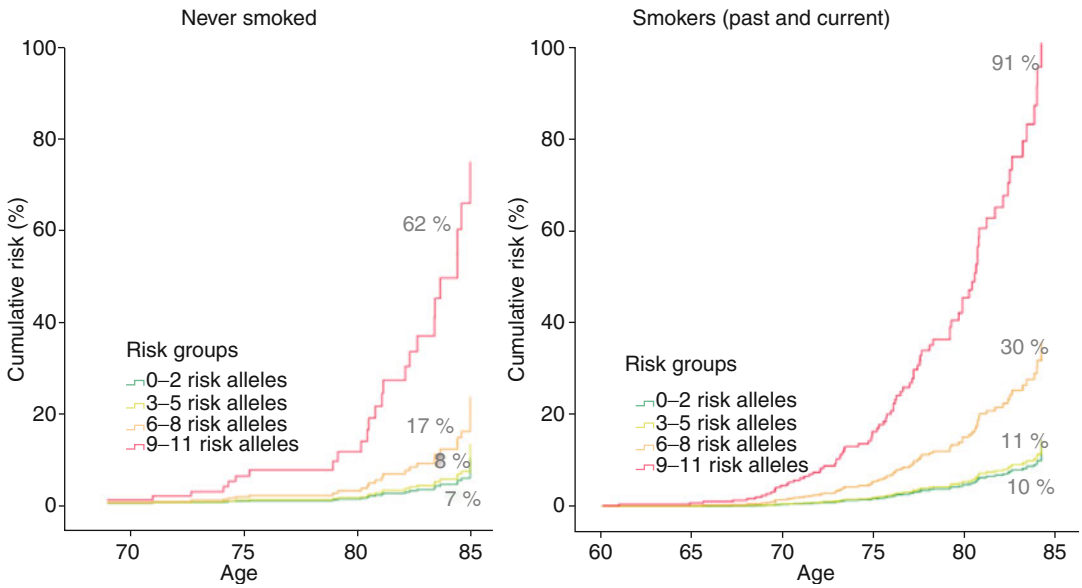


**Fig. 5.2** Absolute risks of late AMD stratified for genetic load and smoking history in the Rotterdam Study

### 5.2.6.3 Risk of AMD Due to the Combined Effect of *CFH* and *ARMS2/HTRA1* SNPs

Several studies have investigated the combined effect of *CFH* Y402H and *ARMS2* A69S/*HTRA1* rs11200638 (Rivera et al. 2005; Yang et al. 2006; Cameron et al. 2007; Schaumberg et al. 2007; Yoshida et al. 2007; Francis et al. 2008; Kaur et al. 2008; Seitsonen et al. 2008; Losonczy et al. 2011). Persons with homozygous risk genotypes at both loci (*CFH* CC – *ARMS2* TT) compared to the non-risk genotype (TTGG) had ORs ranging from 27 in a Finnish case–control study to 228 in the Caucasian clinic-based AREDS. For persons with the homozygous risk genotype for both *CFH* Y402H and *HTRA1* rs11200638, the combined ORs ranged from eight in a Japanese case–control study to 193 in AREDS relative to persons with no risk alleles at either locus. In addition to the combined risk conferred by *CFH* Y402H and *ARMS2* A69S, Schmidt et al. (2006) also observed an extra risk of AMD caused by smoking. Compared to the nonsmoker/TT(Y402H)/GG(A69S) combination, the OR for individuals with the CC-genotype at Y402H and the TT-genotype at *ARMS2* increased from 10.2 for nonsmokers to 34.5 for smokers. Seitsonen et al. (2008) also found that smoking caused an extra risk for AMD but only in connection with sex and *C3* genotype. The univariate ORs for carrying at least one risk allele of *CFH* Y402H was 5.45 (95 % CI, 2.18–16.83), of *ARMS2* A69S was 4.89 (95 % CI, 1.73–16.43), of *C3* R102G was 2.12 (95 % CI, 0.52–8.70), and for smoking was 3.22 (95 % CI 1.81–6.09), while the joint OR for the three loci and smoking was 74.3 (95 % CI, 10.81–2123.6). In the RS the effect of smoking within carriers of several risk variants in the *CFH*, *ARMS2*, *C2/FB*, *C3*, *CFI*, *TIMP3*, *LIPC*, *CETP* was investigated. Carriers of 9-11 risk alleles in these genes who smoked had a risk of 91 % of developing late AMD compared to 62 % for the non smokers with the same amount of risk alleles (Fig. 5.2).

### 5.2.6.4 *APOE* Gene

Debate remains regarding the gender-specific role of the *APOE* alleles in the development or progression of AMD. Schmidt et al. found significant interaction between ε2-carrier status and sex (Schmidt et al. 2002). The ε2 allele conferred a risk of 0.74 (95 % CI, 0.52–1.06) in women and of 1.54 (95 % CI, 0.97–2.45) in men. Hence, the authors suggested that an increased risk of AMD due to the ε2 allele may only be conferred to men. Conversely, Baird et al. (2004) found that ε2 carriers had a significant 4.8-fold (95 % CI, 1.19–19.09) increased risk of AMD progression compared to ε4 carriers and a nearly significant 2.8-fold (95 % CI, 0.96–19.09)

increased risk compared to ε3 carriers. Since this finding was only present in women, the authors suggested that there may be a gender-specific role in progression of AMD in persons with an ε2 allele. Fritsche et al. (2009) could not corroborate any gender-specific role of the *APOE* alleles.

Schmidt et al. (2000, 2005) suggested a modifying effect of *APOE* genotypes on the smoking-associated risk of AMD, particularly for CNV. The effect of smoking was most deleterious for *APOE* ε2 carriers, compared to *APOE* ε4 carriers and persons with the *APOE* ε3/ε3 genotype. The increase in CNV risk due to smoking was greatest in *APOE* ε2 carriers, with genotype-specific risks increasing from 1.9 for *APOE* ε4 carriers ($P=0.11$) to 2.2 for *APOE* ε3/ε3 homozygotes ($P=0.007$) to 4.6 ($P=0.001$) for *APOE* ε2 carriers, compared to non-smoking *APOE* ε3/ε3 persons. In other studies, the sample sizes of each subgroup were too small to determine statistical significance (Zareparsi et al. 2004; Tikellis et al. 2007).

### 5.2.7 Conclusion

Since the first assumption of a familial component to AMD, 15 genes associated with the disease have been identified. These genes have shed light on the pathogenesis of AMD and have increased our knowledge on the causes of AMD enormously.

Most of the genetic risk is explained by only two genes, *CFH* and *ARMS2/HTRA1*. The risk variants in these genes occur at a much higher frequency in the general population than the actual disease does, provoking the view that lifestyle factors ultimately determine whether these genes will have a deleterious effect. Interaction with lifestyle factors such as smoking and BMI has been difficult to prove, but the first reports on the complexity of gene-environment modulations have appeared.

Future genetic research will make use of the new molecular methodology such as exome and whole genome sequencing. This will undoubtedly lead to finding more risk variants and more information on causal pathways for AMD. Large genetic epidemiologic collaborations will be able to address the interaction with environmental factors better than single studies can, and they will also help elucidate AMD pathogenesis. It is expected that these developments will open up new avenues for long-lasting and successful treatments for AMD.

## 5.3 Primary Open-Angle Glaucoma

Familial occurrence of glaucoma has been known for decades; early reports on this topic stem from 1869 (Von Graefe 1869; James 1927). It has been estimated that up to 50 % of POAG patients have a positive family history (Tielsch et al. 1994). The risk for family members was calculated in a population-based familial aggregation study; first degree relatives of an affected individual had an approximately tenfold increased risk of developing POAG compared to first degree relatives of controls (22 % vs. 2.3 %) (Wolfs et al. 1998). During the last two decades, the attention has shifted towards identification of associated genes (Table 5.2). So far, 15 chromosomal regions have been identified for POAG (HGNC Database 2011). Several POAG genes are rare but have a major effect on the risk of disease. Other genes are more common but have only minor effects.

### 5.3.1 Rare Genes with High Risk of POAG

#### 5.3.1.1 *MYOC*

The first gene carrying an important POAG risk was found in a disease-associated locus and named *TIGR* (trabecular meshwork-induced glucocorticoid response protein) or *MYOC* (encoding myocilin) (Sheffield et al. 1993; Stone et al. 1997; Kubota et al. 1997). The name myocilin was chosen because of its similarities with myosin- and olfactomedin-like domains and the abundant appearance in the connecting cilium of photoreceptor cells. Myocilin is expressed in most tissues of the body and in most ocular tissues (including trabecular meshwork, sclera, iris, cornea, lens, ciliary body, retina, optic nerve, and vitreous humor) (Fingert et al. 2002). Mutations in the *MYOC* gene generally lead to an elevated intraocular pressure (IOP). Many

disease mechanisms have been suggested, such as (Polansky et al. 1997) an overproduction of myocilin by the trabecular meshwork with subsequent accumulation causing obstruction in the outflow of aqueous humor and elevated intraocular pressure. Nevertheless, the precise effect of the mutated gene is still unclear (Liu and Allingham. 2011). Myocilin-associated glaucoma inherits as an autosomal dominant disease, and carriers of a mutation have a 90 % risk of developing POAG (Alward et al. 1998). Most mutations are associated with juvenile or early adult onset of POAG, although some are associated with the adult-onset phenotype (GLN368STOP mutation, Fingert et al. 2002). *MYOC* is estimated to play a role in 3–5 % of POAG cases.

#### 5.3.1.2 *OPTN*

The second well-identified gene with a major effect is *OPTN* (encoding optineurin, i.e., "optic neuropathy-inducing" protein) (Sarfarazi et al. 1998; Rezaie et al. 2002). The site of expression of this protein includes the trabecular meshwork, aqueous humor and retina, and the current hypothesis is that its effect is neuroprotective. A defective optineurin increases the susceptibility of retinal ganglion cells to premature death, but the exact mechanisms behind the mutations are unclear (Liu and Allingham. 2011). Mutations in optineurin are associated with normal tension glaucoma. The E50K mutation is the most common mutation, and carriers of E50K have a more severe form of glaucoma (Aung et al. 2005). They are younger at onset, have a worse initial cup-disc ratio, and a faster progression of visual field loss.

#### 5.3.1.3 *WDR36*

The third high-risk gene is *WDR36* (WD40-repeat 36) (Monemi et al. 2005). In the initial study, mutations were found in patients with high- and low-pressure glaucoma. In a study with 118 probands from families affected by POAG, patients with a more severe disease more often had a *WDR36* variant, so it was suggested that *WDR36* acts as modifier gene (Hauser et al. 2006). *WDR36* is expressed in non-ocular and numerous ocular tissues (lens, iris, sclera, ciliary muscles, ciliary body, trabecular meshwork, retina, and optic nerve). The protein WDR36 interacts with P53 (Footz et al. 2009). Mouse models show that mutations in *WDR36* lead to progressive degeneration of retinal ganglion cells in the peripheral retina (Chi et al. 2010), and WDR36 depletions in human trabecular meshwork cells lead to apoptotic cell death (Gallenberger et al. 2011).

#### 5.3.1.4 *NTF4*

A mutation in neurotrophin-4 (*NTF4*) was recorded in 1.7 % of European POAG patients (Pasutto et al. 2009). The most frequent *NTF4* mutation leads to decreased activation of tyrosine kinase receptor B and that may cause loss of neurotrophic function (Liu and Allingham. 2011). *NTF4* mutations are even less frequent in other populations; for instance, it is present in only 0.6 % of Chinese POAG patients (Vithana et al. 2010).

### 5.3.2 Common Genes with Minor Risk of POAG

#### 5.3.2.1 *CAV1/CAV2*

A variant (rs4236601) near the Caveolin 1 and 2 genes was associated with POAG (Thorleifsson et al. 2010). This variant increased the risk of POAG 1.2× in persons of European ancestry but up to 5× in Chinese. In the eye, *CAV1* and *CAV2* are expressed in the scleral spur cells, trabecular meshwork, and retinal ganglion cells. It is unknown how it plays a role in the pathogenesis.

#### 5.3.2.2 *CDKN2B*

This gene was initially discovered as an association with vertical cup-disc ratio (VCDR) (Ramdas et al. 2010). Recently, it was shown that the risk variant in this gene increased the risk of POAG 1.5× (Ramdas et al. 2011a; Burdon et al. 2011). *CDKN2B* encodes a protein which plays a role in cell growth regulation (Ramdas et al. 2010).

#### 5.3.2.3 *ATOH7*

Aside from the involvement in optic disc area and VCDR (Macgregor et al. 2010; Ramdas et al. 2010), risk variants in *ATOH7* are associated with

**Table 5.2** Overview of major genes associated with POAG

| Gene | Location | POAG | VCDR | DA | IOP | Study design | Replication | Gene function | References |
|---|---|---|---|---|---|---|---|---|---|
| *MYOC* | 1q23iq24 | + | ? | ? | ? | Linkage analysis | + | Unclear | Sheffield et al. (1993), Stone et al. (1997) |
| *OPTN* | 10p13 | + | ? | ? | ? | Linkage analysis | + | Loss of neuroprotection in eye and optic nerve | Sarfarazi et al. (1998), Rezaie et al. 2002 |
| *WDR36* | 5q22.1 | + | ? | ? | ? | Mutation screening candidate genes | + | Progressive degeneration of retinal ganglion cells, apoptosis in trabecular meshwork | Monemi et al. (2005), Chi et al. (2010), Gallenberger et al. (2011) |
| *NTF4* | 19q13.3 | + | ? | ? | ? | Mutation screening | + | Loss of neurotrophic function | Pasutto et al. (2009), Vithana et al. (2010) |
| *CAV1/2* | 7q31 | + | ? | ? | ? | GWAS | + | Unknown | Thorleifsson et al. (2010) |
| *CDKN2B* | 9p21 | + | + | ? | ? | GWAS | + | Cell growth regulation | Ramdas et al. (2010) |
| *ATOH7* | 10q21.3-q22.1 | + | + | + | ? | GWAS | + | Retinal ganglion cell and optic nerve formation in mice | Brown et al. (2002), Macgregor et al. (2010), Ramdas et al. (2010, 2011) |
| *SIX1* | 14q22.2-q23 | + | + | ? | ? | GWAS | + | Eye organogenesis | Ramdas et al. (2010, 2011) |
| *TMCO1* | 1q24.1 | + | ? | ? | + | GWAS | + | Unknown. Interacts with CAV1 | Burdon et al. (2011), van Koolwijk et al. (2012) |
| *GAS7* | 17p13.1 | + | ? | ? | + | GWAS | + | Cell remodeling. Interacts with MYOC, OPTN, WDR36, and CAV1 | Van Koolwijk et al. (2012) |
| *RPGRIP1* | 14q11 | + | ? | ? | ? | Mutation screening candidate genes | – | Susceptibility gene. Scaffold for proteins acting in signaling pathways of different retinal cells | Fernandéz-Martínez et al. (2011) |
| *TBK1* | 12q14 | + | ? | ? | ? | Linkage study | + | Interacts with optineurin. Regulation of genes in the NF-kappaB signaling pathway | Fingert et al. (2011), Davis et al. (2011) |
| *ANP* | 1p36.21 | + | ? | ? | ? | Analysis of ANP | – | Regulation of intraocular pressure | Tunny et al. (1996) |
| *APOE* | 19q13.31 | + | ? | ? | ? | Analysis of APOE | ? | Involved in neurodegenerative diseases like Alzheimer's disease | Copin et al. (2002), Vickers et al. (2002), Mabuchi et al. (2005), Lam et al. (2006), Ressiniotis et al. (2004) |
| *TP53* | 17p13.1 | + | ? | ? | ? | Analysis of P53 | ? | Regulation of apoptosis | Lin et al. (2002), Daugherty et al. (2009), Saglar et al. (2009) |
| *OPA1* | 3q28-q29 | + | ? | ? | ? | Analysis of OPA1 | ? | Involved in autosomal dominant optic atrophy | Aung et al. (2002a), Liu et al. (2007) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *CYP1B1* | 2p22.2 | + | ? | ? | ? | Analysis of CYP1B1 | ? | Development of iridocorneal angle | López-Garrido et al. (2006), Bhattacharjee et al. (2008), Pasutto et al. (2010), Burdon et al. (2010) |
| *TNFα* | 6p21.3 | + | ? | ? | ? | Analysis of TNFα | ? | Apoptosis | Lin et al. (2003a, b) |
| *IGF-2* | 11p15.5 | + | ? | ? | ? | Analysis of IGF-2 | – | Regulation of apoptosis | Tsai et al. (2003) |
| *IL1α* | 2q14 | + | ? | ? | ? | Analysis of IL 1α | ? | Apoptosis | Wang et al. (2006), Mookherjee et al. (2010) |
| *IL1β* | 2q14 | + | ? | ? | ? | Analysis of IL 1β | ? | Apoptosis | Lin et al. (2003a, b), Mookherjee et al. (2010) |
| *CDC7* | 1p22 | ? | ? | + | ? | GWAS | + | Cell division cyclus. Interacts with CDKN2A | Ramdas et al. (2010) |
| *TGFBR3* | 1p22 | ? | ? | + | ? | GWAS | + | GDF11 interacts with ATOH7 | Ramdas et al. (2010) |
| *SALL1* | 16q12.1 | ? | ? | + | ? | GWAS | + | Involved in branchio-oto-renal syndrome and Townes-Brocks syndrome | Ramdas et al. (2010) |
| *CARD10* | 22q13.1 | ? | ? | + | ? | GWAS | + | Regulation of apoptosis. Signals the activation of NF-kappaB | Khor et al. (2011) |
| *SCYL1* | 11q11-q12 | ? | + | ? | ? | GWAS | + | Associated with optic nerve atrophy in mice | Ramdas et al. (2010) |
| *LTBP3* | 11q12 | ? | + | ? | ? | GWAS | + | Cell growth regulation | Ramdas et al. (2010) |
| *DCLK1* | 13q13 | ? | + | ? | ? | GWAS | + | Calcium signaling pathway which controls neuronal migration in developing and mature brain | Ramdas et al. (2010) |
| *CHEK2* | 22q12.1 | ? | + | ? | ? | GWAS | + | Associated with several types of cancer | Ramdas et al. (2010) |
| *RERE* | 1p36 | ? | + | ? | ? | GWAS, linkage and association analysis | + | Apoptosis via triggering of caspase-3 activation | Ramdas et al. (2010), Axenovich et al. (2011) |
| *LRP1B* | 2q21.2-q22.2 | ? | + | ? | ? | GWAS, linkage and association analysis | + | Developing of the eye | Macgregor et al. (2010), Axenovich et al. (2011) |

*POAG* primary open-angle glaucoma, *VCDR* vertical cup-disc ratio, *DA* disc area, *IOP* intraocular pressure, *GWAS* genome wide association study. Symbols in "replication" column: + replicated, – not replicated, ? controversial

a 1.3× increased risk of POAG (Ramdas et al. 2011a). *ATOH7* is expressed in the retina and plays a role in retinal ganglion cell and optic nerve formation in mice (Brown et al. 2002), but it has not been linked to optic nerve pathology in humans (Ramdas et al. 2011a).

#### 5.3.2.4 *SIX1*

A locus between SIX1 and SIX6 is associated with vertical cup-disc ratio and a 1.2× increased risk of POAG (Ramdas et al. 2010, 2011a). Variants in SIX6 are associated with bronchio-oto-renal syndrome. *SIX1* plays a role in eye organogenesis.

#### 5.3.2.5 *TMCO1*

SNPs located in *TMCO1* are significantly associated with intraocular pressure and a 1.3× increased risk of glaucoma (Burdon et al. 2011; van Koolwijk et al. 2012). The function of *TMCO1* is largely unknown. It is highly expressed in the human ciliary body and trabecular meshwork and interacts with CAV1.

#### 5.3.2.6 *GAS7*

*GAS7* has been associated with intraocular pressure and a 10 % decreased glaucoma risk (van Koolwijk et al. 2012). *GAS7* is expressed in the ciliary body and the human trabecular meshwork. It is implicated in cell remodeling. The gene interacts with *MYOC* and other known glaucoma genes such as *OPTN*, *WDR36*, and *CAV1*.

#### 5.3.2.7 *RPGRIP1*

Associations between retinitis pigmentosa GTPase regulator-interacting protein 1 (*RPGRIP1*) and POAG have been found in European subjects (Fernandéz-Martínez et al. 2011). RPGRIP1 is a scaffold for proteins acting in signaling pathways of different retinal cells. The gene may act as a susceptibility gene.

#### Copy Number Variations

Fingert et al. (2011) and Davis et al. (2011) reported about the association between copy number variations (CNVs) and POAG. Fingert et al. identified a new chromosomal POAG locus and suggested that an extra copy of the TBK1 gene on this region (chromosome 12q14) is responsible for their normal tension glaucoma cases. It was expressed in microvasculature of the retina, the nerve fiber layer, and in ganglion cells. In interacts with optineurin. Further, a kinase encoded by *TBK1* regulates the expression of genes involved in the NF-kappaB signaling pathway. Processes regulated by this pathway, e.g., apoptosis, have been implicated in the pathogenesis of glaucoma.

#### Spurious Candidates

Many other genetic variants have been related to POAG, but their association is less clear-cut than the genes mentioned above. Tunny et al. (1996) suggested that mutations in the atrial natriuretic peptide (*ANP*) gene may play a role in at least a proportion of patients with familial glaucoma due to regulation of intraocular pressure.

An association between POAG and apolipoprotein E (*APOE*) was suggested in French, Tasmania, Japanese, and Chinese populations (Copin et al. 2002; Vickers et al. 2002; Mabuchi et al. 2005; Lam et al. 2006). *APOE* has been involved in Alzheimer's disease, like glaucoma a neurodegenerative disease. Patients with Alzheimer's disease have an increased frequency of glaucoma. Functionally, *APOE* is known to interact with myocilin. Although these are interesting findings for the pathogenesis of glaucoma, the role of *APOE* remains controversial (Ressiniotis et al. 2004).

Glaucomatous neuropathy is caused by apoptosis. Tumor suppressor protein p53 plays a role in regulation of apoptosis, and it has been suggested that variants in p53 are a risk factor in the development of POAG in Chinese and Caucasian populations (Lin et al. 2002; Daugherty et al. 2009).

Polymorphisms in *OPA1* have been associated with normal tension glaucoma (Aung et al. 2002a, b), but it seems that this is not the case in glaucoma phenotypes with elevated intraocular pressure (Liu et al. 2007).

An association between *CYP1B1* and POAG is also controversial (López-Garrido et al. 2006; Bhattacharjee et al. 2008; Pasutto et al. 2010; Burdon et al. 2010). Several other variants have been described, such as variants in tumor necrosis factor alpha (Lin et al. 2003a), insulin-like growth factor 2 (Tsai et al. 2003), interleukin-1 beta (Lin et al. 2003b), and interleukin-1 alpha

(Wang et al. 2006). However, most have not been replicated by other investigators or in other populations (Allingham et al. 2009).

### 5.3.3 Genes Associated with POAG Intermediates

An approach that has been recently used in the identification of POAG genes is the focus on quantitative intermediate POAG outcomes, such as VCDR and IOP. The heritability for VCDR ranges from 0.48 to 0.80 and for IOP from 0.29 to 0.50 (Schwartz et al. 1975; Chang et al. 2005; Klein et al. 2004; van Koolwijk et al. 2007). Several genes that could be validated as glaucoma genes have been discovered in this way (*CDKN2B*, *ATOH7*, *SIX1*, *TMCO1*, and *GAS7*; see above). So, up to now, this approach appears to be successful.

### 5.3.4 Optic Disc Area

SNPs in or near the genes *CDC7*, *TGFBR3*, *SALL1*, and *CARD10* have been associated with optic disc area (Ramdas et al. 2010; Khor et al. 2011). *CDC7* encodes a protein which is involved in cell division cyclus. This protein also interacts with the CDKN2A protein which is associated with VCDR. A member of the bone morphogenetic protein (BMP) and TGFbeta superfamily is *GDF11*. This gene is of the same family as *TGFBR3* and interacts with *ATOH7*. *SALL1* defects are a cause of the branchio-oto-renal syndrome and Townes-Brocks syndrome. Ocular manifestations of the latter include optic nerve atrophy (Barry and Reddy 2008). *CARD10* is involved in the regulation of apoptosis and signals the activation of NF-kappaB. The NF-kappaB signaling pathway is implicated in major neurodegenerative diseases like Alzheimer's disease.

### 5.3.5 Vertical Cup-Disc Ratio

Associations with vertical cup-disc ratio were found for loci between *FRMD8*, *SCYL1*, and *LTBP3* in the *DCLK1* gene, *CHEK2* gene, *RERE* gene, and *LRP1B* gene (Ramdas et al. 2010; Macgregor et al. 2010; Axenovich et al. 2011). *SCYL1* has been associated with optic nerve atrophy in mice. *LTBP3* is involved in the same signaling pathway as *CDKN2B* for cell growth regulation. It is also homolog to *LTBP2*, which is implicated in primary congenital glaucoma. *DLCK1* may be involved in a calcium signaling pathway. This pathway controls neuronal migration in developing brain and mature brain. Several types of cancer are associated with *CHEK2*. Overexpression of *RERE* leads to apoptosis via triggering of caspase-3 activation. *LRP1B* may be included in a development pathway (with *SIX1*, *SALL1* and *DCLK1*).

**Conclusion**

A variety of genes have been implicated in the pathogenesis of POAG. Their effect is one of extremes. On one end are mutations in the *MYOC*, *OPTN*, and *WDR36* genes with a large impact on the risk of POAG; however, they occur only in a small number of families. On the other end are frequent variants with only small effects. All mutations in the currently six established POAG genes combined (*MYOC*, *OPTN*, *WDR36*, *ATOH7*, *CDKN2B*, and *SIX1*) explain, together with age, gender and IOP, only 4–6 % of the variation in POAG risk (Ramdas et al. 2011b). Hence, there is still much work to do in unraveling the genetic background of this disease.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Abecasis GR, Yashar BM, Zhao Y et al (2004) Age-related macular degeneration: a high-resolution genome scan for susceptibility loci in a population enriched for late-stage disease. Am J Hum Genet 74:482–494

Allingham RR, Liu Y, Rhee DJ (2009) The genetics of primary open-angle glaucoma: a review. Exp Eye Res 88:837–844

Alward WL, Fingert JH, Coote MA et al (1998) Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). N Engl J Med 338:1022–1027

Anderson DH, Ozaki S, Nealon M et al (2001) Local cellular sources of apolipoprotein E in the human retina and retinal pigmented epithelium: implications for the process of drusen formation. Am J Ophthalmol 131: 767–781

Anderson DH, Talaga KC, Rivest AJ et al (2004) Characterization of beta amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. Exp Eye Res 78:243–256

Arakawa S, Takahashi A, Ashikawa K et al (2011) Genome-wide association study identifies two susceptibility loci for exudative age-related macular degeneration in the Japanese population. Nat Genet 43: 1001–1004

Aung T, Ocaka L, Ebenezer ND et al (2002a) A major marker for normal tension glaucoma: association with polymorphisms in the OPA1 gene. Hum Genet 110: 52–56

Aung T, Ocaka L, Ebenezer ND et al (2002b) Investigating the association between OPA1 polymorphisms and glaucoma: comparison between normal tension and high tension primary open angle glaucoma. Hum Genet 110:513–514

Aung T, Rezaie T, Okada K et al (2005) Clinical features and course of patients with glaucoma with the E50K mutation in the optineurin gene. Invest Ophthalmol Vis Sci 46:2816–2822

Austin MA, Zhang C, Humphries SE et al (2004) Heritability of C-reactive protein and association with apolipoprotein E genotypes in Japanese Americans. Ann Hum Genet 68:179–188

Axenovich T, Zorkoltseva I, Belonogova N et al (2011) Linkage and association analyses of glaucoma related traits in a large pedigree from a Dutch genetically isolated population. J Med Genet 48:802–809

Baird PN, Guida E, Chu DT et al (2004) The epsilon2 and epsilon4 alleles of the apolipoprotein gene are associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 45:1311–1315

Baird PN, Islam FM, Richardson AJ et al (2006a) Analysis of the Y402H variant of the complement factor H gene in age-related macular degeneration. Invest Ophthalmol Vis Sci 47:4194–4198

Baird PN, Richardson AJ, Robman LD et al (2006b) Apolipoprotein (APOE) gene is associated with progression of age-related macular degeneration (AMD). Hum Mutat 27:337–342

Barron MJ, Johnson MA, Andrews RM et al (2001) Mitochondrial abnormalities in ageing macular photoreceptors. Invest Ophthalmol Vis Sci 42:3016–3022

Barry JS, Reddy MA (2008) The association of an epibulbar dermoid and Duane syndrome in a patient with a SALL1 mutation (Townes-Brocks Syndrome). Ophthalmic Genet 29:177–180

Bergeron-Sawitzke J, Gold B, Olsh A et al (2009) Multilocus analysis of age-related macular degeneration. Eur J Hum Genet 17:1190–1199

Bhattacharjee A, Banerjee D, Mookherjee S et al (2008) Leu432Val polymorphism in CYP1B1 as a susceptible factor towards predisposition to primary open-angle glaucoma. Mol Vis 14:841–850

Bojanowski CM, Shen D, Chew EY et al (2006) An apolipoprotein E variant may protect against age-related macular degeneration through cytokine regulation. Environ Mol Mutagen 47:594–602

Brantley MA Jr, Fang AM, King JM et al (2007) Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to intravitreal bevacizumab. Ophthalmology 114:2168–2173

Brown NL, Dagenais SL, Chen CM et al (2002) Molecular characterization and mapping of ATOH7, a human atonal homolog with a predicted role in retinal ganglion cell development. Mamm Genome 13:95–101

Burdon KP, Hewitt AW, Mackey DA et al (2010) Tag SNPs detect association of the CYP1B1 gene with primary open angle glaucoma. Mol Vis 16:2286–2293

Burdon KP, Macgregor S, Hewitt AW et al (2011) Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. Nat Genet 43:574–578

Cameron DJ, Yang Z, Gibbs D et al (2007) HTRA1 variant confers similar risks to geographic atrophy and neovascular age-related macular degeneration. Cell Cycle 6:1122–1125

Cann HM, de Toma C, Cazes L et al (2002) A human genome diversity cell line panel. Science 296:261–262

Chan CC, Shen D, Zhou M et al (2007) Human HtrA1 in the archived eyes with age-related macular degeneration. Trans Am Ophthalmol Soc 105:92–97; discussion 97–98

Chang TC, Congdon NG, Wojciechowski R et al (2005) Determinants and heritability of intraocular pressure and cup-to-disc ratio in a defined older population. Ophthalmology 112:1186–1191

Chen LJ, Liu DT, Tam PO et al (2006) Association of complement factor H polymorphisms with exudative age-related macular degeneration. Mol Vis 12:1536–1542

Chen W, Xu W, Tao Q et al (2009) Meta-analysis of the association of the HTRA1 polymorphisms with the risk of age-related macular degeneration. Exp Eye Res 89:292–300

Chen W, Stambolian D, Edwards AO et al (2010) Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. Proc Natl Acad Sci USA 107:7401–7406

Chi ZL, Yasumoto F, Sergeev Y et al (2010) Mutant WDR36 directly affects axon growth of retinal ganglion cells leading to progressive retinal degeneration in mice. Hum Mol Genet 19:3806–3815

Chowers I, Cohen Y, Goldenberg-Cohen N et al (2008a) Association of complement factor H Y402H polymorphism with phenotype of neovascular age related macular degeneration in Israel. Mol Vis 14:1829–1834

Chowers I, Meir T, Lederman M et al (2008b) Sequence variants in HTRA1 and LOC387715/ARMS2 and phenotype and response to photodynamic therapy in neovascular age-related macular degeneration in populations from Israel. Mol Vis 14:2263–2271

Chu J, Zhou CC, Lu N et al (2008) Genetic variants in three genes and smoking show strong associations with susceptibility to exudative age-related macular

degeneration in a Chinese population. Chin Med J 121:2525–2533
Conley YP, Jakobsdottir J, Mah T et al (2006) CFH, ELOVL4, PLEKHA1 and LOC387715 genes and susceptibility to age-related maculopathy: AREDS and CHS cohorts and meta-analyses. Hum Mol Genet 15:3206–3218
Copin B, Brézin AP, Valtot F et al (2002) Apolipoprotein E–promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. Am J Hum Genet 70:1575–1581
Crabb JW, Miyagi M, Gu X et al (2002) Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. Proc Natl Acad Sci USA 99:14682–14687
Cui L, Zhou H, Yu J et al (2010) Noncoding variant in the complement factor H gene and risk of exudative age-related macular degeneration in a Chinese population. Invest Ophthalmol Vis Sci 51:1116–1120
Curcio CA, Presley JB, Malek G et al (2005) Esterified and unesterified cholesterol in drusen and basal deposits of eyes with age-related maculopathy. Exp Eye Res 81:731–741
Daugherty CL, Curtis H, Realini T et al (2009) Primary open angle glaucoma in a Caucasian population is associated with the p53 codon 72 polymorphism. Mol Vis 15:1939–1944
Davis LK, Meyer KJ, Schindler EL et al (2011) Copy number variations and primary open-angle glaucoma. Invest Ophthalmol Vis Sci 52:7122–7133
De La Paz MA, Pericak-Vance MA, Lennon F et al (1997) Exclusion of TIMP3 as a candidate locus in age-related macular degeneration. Invest Ophthalmol Vis Sci 38:1060–1065
Deangelis MM, Ji F, Kim IK et al (2007) Cigarette smoking, CFH, APOE, ELOVL4, and risk of neovascular age-related macular degeneration. Arch Ophthalmol 125:49–54
Deangelis MM, Ji F, Adams S et al (2008) Alleles in the HtrA serine peptidase 1 gene alter the risk of neovascular age-related macular degeneration. Ophthalmology 115:1209–1215
Delcourt C, Delyfer MN, Rougier MB et al (2011) Associations of complement factor h and smoking with early age-related macular degeneration: the ALIENOR study. Invest Ophthalmol Vis Sci 52:5955–5962
Despriet DD, Klaver CC, Witteman JC et al (2006) Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA 296:301–309
Despriet DD, Klaver CC, van Duijn CM et al (2007) Predictive value of multiple genetic testing for age-related macular degeneration. Arch Ophthalmol 125:1270–1271
Despriet DD, van Duijn CM, Oostra BA et al (2009) Complement component C3 and risk of age-related macular degeneration. Ophthalmology 116(474–480):e2
Dewan A, Liu M, Hartman S et al (2006) HTRA1 promoter polymorphism in wet age-related macular degeneration. Science 314:989–992
Droz I, Mantel I, Ambresin A et al (2008) Genotype-phenotype correlation of age-related macular degeneration: influence of complement factor H polymorphism. Br J Ophthalmol 92:513–517
Edwards AO, Ritter R III, Abel KJ et al (2005) Complement factor H polymorphism and age-related macular degeneration. Science 308:421–424
Edwards AO, Fridley BL, James KM et al (2008) Evaluation of clustering and genotype distribution for replication in genome wide association studies: the age-related eye disease study. PLoS One 3:e3813
Eiriksdottir G, Aspelund T, Bjarnadottir K et al (2006) Apolipoprotein E genotype and statins affect CRP levels through independent and different mechanisms: AGES Reykjavik Study. Atherosclerosis 186:222–224
Ennis S, Gibson J, Cree AJ et al (2010) Support for the involvement of complement factor I in age-related macular degeneration. Eur J Hum Genet 18:15–16
Evans DA, Beckett LA, Field TS et al (1997) Apolipoprotein E epsilon4 and incidence of Alzheimer disease in a community population of older persons. JAMA 277:822–824
Fagerness JA, Maller JB, Neale BM et al (2009) Variation near complement factor I is associated with risk of advanced AMD. Eur J Hum Genet 17:100–104
Fauser S, Smailhodzic D, Caramoy A et al (2011) Evaluation of serum lipid concentrations and genetic variants at high-density lipoprotein metabolism loci and TIMP3 in age-related macular degeneration. Invest Ophthalmol Vis Sci 52:5525–5528
Feher J, Kovacs I, Artico M et al (2006) Mitochondrial alterations of retinal pigment epithelium in age-related macular degeneration. Neurobiol Aging 27:983–993
Felbor U, Doepner D, Schneider U et al (1997) Evaluation of the gene encoding the tissue inhibitor of metalloproteinases-3 in various maculopathies. Invest Ophthalmol Vis Sci 38:1054–1059
Fernandéz-Martínez L, Letteboer S, Mardin CY et al (2011) Evidence for RPGRIP1 gene as risk factor for primary open angle glaucoma. Eur J Hum Genet 19: 445–451
Fingert JH, Stone EM, Sheffield VC et al (2002) Myocilin glaucoma. Surv Ophthalmol 47:547–561
Fingert JH, Robin AL, Stone JL et al (2011) Copy number variations on chromosome 12q14 in patients with normal tension glaucoma. Hum Mol Genet 20:2482–2494
Fisher SA, Abecasis GR, Yashar BM et al (2005) Meta-analysis of genome scans of age-related macular degeneration. Hum Mol Genet 14:2257–2264
Fisher SA, Rivera A, Fritsche LG et al (2007) Assessment of the contribution of CFH and chromosome 10q26 AMD susceptibility loci in a Russian population isolate. Br J Ophthalmol 91:576–578
Footz TK, Johnson JL, Dubois S et al (2009) Glaucoma-associated WDR36 variants encode functional defects in a yeast model system. Hum Mol Genet 18: 1276–1287
Francis PJ, George S, Schultz DW et al (2007) The LOC387715 gene, smoking, body mass index, environmental associations with advanced age-related macular degeneration. Hum Hered 63:212–218

Francis PJ, Zhang H, Dewan A et al (2008) Joint effects of polymorphisms in the HTRA1, LOC387715/ARMS2, and CFH genes on AMD in a Caucasian population. Mol Vis 14:1395–1400

Francis PJ, Hamon SC, Ott J et al (2009) Polymorphisms in C2, CFB and C3 are associated with progression to advanced age related macular degeneration associated with visual loss. J Med Genet 46:300–307

Fritsche LG, Loenhardt T, Janssen A et al (2008) Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. Nat Genet 40:892–896

Fritsche LG, Freitag-Wolf S, Bettecken T et al (2009) Age-related macular degeneration and functional promoter and coding variants of the apolipoprotein E gene. Hum Mutat 30(7):1048–1053

Fuse N, Miyazawa A, Mengkegale M et al (2006) Polymorphisms in Complement Factor H and Hemicentin-1 genes in a Japanese population with dry-type age-related macular degeneration. Am J Ophthalmol 142:1074–1076

Gallenberger M, Meinel DM, Kroeber M et al (2011) Lack of WDR36 leads to preimplantation embryonic lethality in mice and delays the formation of small subunit ribosomal RNA in human cells in vitro. Hum Mol Genet 20:422–435

Gao Y, Li Y, Xu L et al (2010) Complement factor H polymorphism in age-related maculopathy in the Chinese population: the Beijing Eye Study. Retina 30:443–446

Gibbs D, Yang Z, Constantine R et al (2008) Further mapping of 10q26 supports strong association of HTRA1 polymorphisms with age-related macular degeneration. Vision Res 48:685–689

Gold B, Merriam JE, Zernant J et al (2006) Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet 38:458–462

Gotoh N, Kuroiwa S, Kikuchi T et al (2004) Apolipoprotein E polymorphisms in Japanese patients with polypoidal choroidal vasculopathy and exudative age-related macular degeneration. Am J Ophthalmol 138:567–573

Grindle CF, Marshall J (1978) Ageing changes in Bruch's membrane and their functional implications. Trans Ophthalmol Soc U K 98:172–175

Hageman GS, Luthert PJ, Victor Chong NH et al (2001) An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res 20:705–732

Hageman GS, Anderson DH, Johnson LV et al (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci USA 102:7227–7232

Haines JL, Hauser MA, Schmidt S et al (2005) Complement factor H variant increases the risk of age-related macular degeneration. Science 308:419–421

Haines JL, Schnetz-Boutaud N, Schmidt S et al (2006) Functional candidate genes in age-related macular degeneration: significant association with VEGF, VLDLR, and LRP6. Invest Ophthalmol Vis Sci 47:329–335

Hasham SN, Pillarisetti S (2006) Vascular lipases, inflammation and atherosclerosis. Clin Chim Acta 372:179–183

Hauser MA, Allingham RR, Linkroum K et al (2006) Distribution of WDR36 DNA sequence variants in patients with primary open-angle glaucoma. Invest Ophthalmol Vis Sci 47:2542–2546

HGNC Database, HUGO Gene Nomenclature Committee (HGNC), EMBL Outstation – Hinxton, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK www.genenames.org. Dec 2011

Ho L, van Leeuwen R, Witteman JCM et al (2011) Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and ω-3 fatty acids. Arch Ophthalmol 129:758–766

Hughes AE, Orr N, Esfandiary H et al (2006) A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nat Genet 38:1173–1177

Hughes AE, Orr N, Patterson C et al (2007) Neovascular age-related macular degeneration risk based on CFH, LOC387715/HTRA1, and smoking. PLoS Med 4:e355

Ignatius MJ, Gebicke-Harter PJ, Skene JH et al (1986) Expression of apolipoprotein E during nerve degeneration and regeneration. Proc Natl Acad Sci USA 83:1125–1129

Ishida BY, Bailey KR, Duncan KG et al (2004) Regulated expression of apolipoprotein E by human retinal pigment epithelial cells. J Lipid Res 45:263–271

Iyengar SK, Song D, Klein BE et al (2004) Dissection of genome-wide scan data in extended families reveals a major locus and oligogenic susceptibility for age-related macular degeneration. Am J Hum Genet 74: 20–39

Jakobsdottir J, Conley YP, Weeks DE et al (2005) Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet 77:389–407

Jakobsdottir J, Conley YP, Weeks DE et al (2008) C2 and CFB genes in age-related maculopathy and joint action with CFH and LOC387715 genes. PLoS One 3:e2199

James RR (1927) A pedigree of a family showing hereditary glaucoma. Br J Ophthalmol 11:438–443

Janssen BJ, Christodoulidou A, McCarthy A et al (2006) Structure of C3b reveals conformational changes that underlie complement activity. Nature 444:213–216

Jarrett SG, Lin H, Godley BF et al (2008) Mitochondrial DNA damage and its potential role in retinal degeneration. Prog Retin Eye Res 27:596–607

Jarvik GP (1997) Genetic predictors of common disease: apolipoprotein E genotype as a paradigm. Ann Epidemiol 7:357–362

Johnson LV, Leitner WP, Staples MK et al (2001) Complement activation and inflammatory processes in drusen formation and age related macular degeneration. Exp Eye Res 73:887–896

Johnson PT, Betts KE, Radeke MJ et al (2006) Individuals homozygous for the age-related macular degeneration

risk-conferring variant of complement factor H have elevated levels of CRP in the choroid. Proc Natl Acad Sci USA 103:17456–17461

Judson R, Brain C, Dain B et al (2004) New and confirmatory evidence of an association between APOE genotype and baseline C-reactive protein in dyslipidemic individuals. Atherosclerosis 177:345–351

Kanda A, Chen W, Othman M et al (2007) A variant of mitochondrial protein LOC387715/ARMS2, not HTRA1, is strongly associated with age-related macular degeneration. Proc Natl Acad Sci USA 104: 16227–16232

Kathiresan S, Willer CJ, Peloso GM et al (2009) Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet 41:56–65

Katsuya T, Baba S, Ishikawa K et al (2002) Epsilon 4 allele of apolipoprotein E gene associates with lower blood pressure in young Japanese subjects: the Suita Study. J Hypertens 20:2017–2021

Kaur I, Katta S, Hussain A et al (2008) Variants in the 10q26 gene cluster (LOC387715 and HTRA1) exhibit enhanced risk of age-related macular degeneration along with CFH in Indian patients. Invest Ophthalmol Vis Sci 49:1771–1776

Kaur I, Katta S, Reddy RK et al (2010) The involvement of complement factor B and complement component C2 in an Indian cohort with age-related macular degeneration. Invest Ophthalmol Vis Sci 51:59–63

Kenealy SJ, Schmidt S, Agarwal A et al (2004) Linkage analysis for age-related macular degeneration supports a gene on chromosome 10q26. Mol Vis 10:57–61

Khor CC, Ramdas WD, Vithana EN et al (2011) Genome-wide association studies in Asians confirm the involvement of ATOH7 and TGFBR3, and further identify CARD10 as a novel locus influencing optic disc area. Hum Mol Genet 20:1864–1872

Kim IK, Ji F, Morrison MA et al (2008) Comprehensive analysis of CRP, CFH Y402H and environmental risk factors on risk of neovascular age-related macular degeneration. Mol Vis 14:1487–1495

Klaver CC, Kliffen M, van Duijn CM et al (1998) Genetic association of apolipoprotein E with age-related macular degeneration. Am J Hum Genet 63:200–206

Klein BEK, Klein R, Lee KE (2004) Heritability of risk factors for primary open-angle glaucoma: the Beaver Dam Eye Study. Invest Ophthalmol Vis Sci 45:59–62

Klein RJ, Zeiss C, Chew EY et al (2005) Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389

Klein ML, Francis PJ, Rosner B et al (2008) CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. Ophthalmology 115:1019–1025

Kondo N, Bessho H, Honda S et al (2010) Additional evidence to support the role of a common variant near the complement factor I gene in susceptibility to age-related macular degeneration. Eur J Hum Genet 18: 634–635

Kortvely E, Hauck SM, Duetsch G et al (2010) ARMS2 is a constituent of the extracellular matrix providing a link between familial and sporadic age-related macular degenerations. Invest Ophthalmol Vis Sci 51:79–88

Kubota R, Noda S, Wang Y et al (1997) A novel myosin-like protein (Myocilin) expressed in the connecting cilium of the photoreceptor: molecular cloning, tissue expression, and chromosomal mapping. Genomics 41:360–369

Laine M, Jarva H, Seitsonen S et al (2007) Y402H polymorphism of complement factor H affects binding affinity to C-reactive protein. J Immunol 178:3831–3836

Lam CY, Fan BJ, Wang DY et al (2006) Association of apolipoprotein E polymorphisms with normal tension glaucoma in a Chinese population. J Glaucoma 15: 218–222

Lau LI, Chen SJ, Cheng CY et al (2006) Association of the Y402H polymorphism in complement factor H gene and neovascular age-related macular degeneration in Chinese patients. Invest Ophthalmol Vis Sci 47:3242–3246

Lee SJ, Kim JH, Chung MJ et al (2007) Human apolipoprotein E2 transgenic mice show lipid accumulation in retinal pigment epithelium and altered expression of VEGF and bFGF in the eyes. J Microbiol Biotechnol 17:1024–1030

Lee SJ, Kim NR, Chin HS (2010) LOC387715/HTRA1 polymorphisms, smoking, and combined effects on exudative age-related macular degeneration in a Korean population. Clin Experiment Ophthalmol 38: 698–704

Li CM, Clark ME, Chimento MF et al (2006a) Apolipoprotein localization in isolated drusen and retinal apolipoprotein gene expression. Invest Ophthalmol Vis Sci 47:3119–3128

Li M, Atmaca-Sonmez P, Othman M et al (2006b) CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. Nat Genet 38:1049–1054

Liang FQ, Godley BF (2003) Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: a possible mechanism for RPE aging and age-related macular degeneration. Exp Eye Res 76:397–403

Lin HJ, Chen WC, Tsai FJ et al (2002) Distributions of p53 codon 72 polymorphism in primary open angle glaucoma. Br J Ophthalmol 86:767–770

Lin HJ, Tsai FJ, Chen WC et al (2003a) Association of tumour necrosis factor alpha-308 gene polymorphism with primary open-angle glaucoma in Chinese. Eye 17:31–34

Lin HJ, Tsai SC, Tsai FJ et al (2003b) Association of interleukin 1beta and receptor antagonist gene polymorphisms with primary open-angle glaucoma. Ophthalmologica 217:358–364

Liu Y, Allingham RR (2011) Molecular genetics in glaucoma. Exp Eye Res 93:331–339

Liu Y, Schmidt S, Qin X et al (2007) No association between OPA1 polymorphisms and primary open-angle glaucoma in three different populations. Mol Vis 13:2137–2141

Liu X, Zhao P, Tang S et al (2010) Association study of complement factor H, C2, CFB, and C3 and age-related macular degeneration in a Han Chinese population. Retina 30:1177–1184

Lokki ML, Koskimies SA (1991) Allelic differences in hemolytic activity and protein concentration of BF molecules are found in association with particular HLA haplotypes. Immunogenetics 34:242–246

López-Garrido MP, Sánchez-Sánchez F, López-Martínez F et al (2006) Heterozygous CYP1B1 gene mutations in Spanish patients with primary open-angle glaucoma. Mol Vis 12:748–755

Losonczy G, Fekete A, Voko Z et al (2011) Analysis of complement factor H Y402H, LOC387715, HTRA1 polymorphisms and ApoE alleles with susceptibility to age related macular degeneration in Hungarian patients. Acta Ophthalmol 89:255–262

Mabuchi F, Tang S, Ando D et al (2005) The apolipoprotein E gene polymorphism is associated with open angle glaucoma in the Japanese population. Mol Vis 11:609–612

Macgregor S, Hewitt AW, Hysi PG et al (2010) Genome-wide association identifies ATOH7 as a major gene determining human optic disc size. Hum Mol Genet 19:2716–2724

Magnusson KP, Duan S, Sigurdsson H et al (2006) CFH Y402H confers similar risk of soft drusen and both forms of advanced AMD. PLoS Med 3:e5

Mahley RW (1988) Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 240:622–630

Majewski J, Schultz DW, Weleber RG et al (2003) Age-related macular degeneration – a genome scan in extended families. Am J Hum Genet 73:540–550

Malek G, Johnson LV, Mace BE et al (2005) Apolipoprotein E allele-dependent pathogenesis: a model for age-related retinal degeneration. Proc Natl Acad Sci USA 102:11900–11905

Maller J, George S, Purcell S et al (2006) Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. Nat Genet 38:1055–1059

Maller JB, Fagerness JA, Reynolds RC et al (2007) Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet 39:1200–1201

Manttari M, Manninen V, Palosuo T et al (2001) Apolipoprotein E polymorphism and C-reactive protein in dyslipidemic middle-aged men. Atherosclerosis 156:237–238

Marz W, Scharnagl H, Hoffmann MM et al (2004) The apolipoprotein E polymorphism is associated with circulating C-reactive protein (the Ludwigshafen risk and cardiovascular health study). Eur Heart J 25: 2109–2119

Mathura JR Jr, Jafari N, Chang JT et al (2000) Bone morphogenetic proteins-2 and -4: negative growth regulators in adult retinal pigmented epithelium. Invest Ophthalmol Vis Sci 41:592–600

McKay GJ, Silvestri G, Patterson CC et al (2009) Further assessment of the complement component 2 and factor B region associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 50:533–539

McKay GJ, Dasari S, Patterson CC et al (2010) Complement component 3: an assessment of association with AMD and analysis of gene-gene and gene-environment interactions in a Northern Irish cohort. Mol Vis 16:194–199

Monemi S, Spaeth G, DaSilva A et al (2005) Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. Hum Mol Genet 14:725–733

Montes T, Tortajada A, Morgan BP et al (2009) Functional basis of protection against age-related macular degeneration conferred by a common polymorphism in complement factor B. Proc Natl Acad Sci USA 106:4366–4371

Mookherjee S, Banerjee D, Chakraborty S et al (2010) Association of IL1A and IL1B loci with primary open angle glaucoma. BMC Med Genet. doi:10.1186/1471-2350-11-99

Mori K, Gehlbach PL, Kabasawa S et al (2007) Coding and noncoding variants in the CFH gene and cigarette smoking influence the risk of age-related macular degeneration in a Japanese population. Invest Ophthalmol Vis Sci 48:5315–5319

Mullins RF, Russell SR, Anderson DH et al (2000) Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J 14:835–846

Neale BM, Fagerness J, Reynolds R et al (2010) Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). Proc Natl Acad Sci USA 107:7395–7400

Neuner B, Wellmann J, Dasch B et al (2008) LOC387715, smoking and their prognostic impact on visual functional status in age-related macular degeneration – The muenster Aging and Retina Study (MARS) cohort. Ophthalmic Epidemiol 15:148–154

Ng TK, Chen LJ, Liu DT et al (2008) Multiple gene polymorphisms in the complement factor H gene are associated with exudative age-related macular degeneration in Chinese. Invest Ophthalmol Vis Sci 49:3312–3317

Nishida N, Walz T, Springer TA (2006) Structural transitions of complement component C3 and its activation products. Proc Natl Acad Sci USA 103:19737–19742

Nonyane BA, Nitsch D, Whittaker JC et al (2010) An ecological correlation study of late age-related macular degeneration and the complement factor H Y402H polymorphism. Invest Ophthalmol Vis Sci 51:2393–2402

Nozaki M, Raisler BJ, Sakurai E et al (2006) Drusen complement components C3a and C5a promote choroidal neovascularization. Proc Natl Acad Sci USA 103: 2328–2333

Oka C, Tsujimoto R, Kajikawa M et al (2004) HtrA1 serine protease inhibits signaling mediated by TGFbeta family proteins. Development 131:1041–1053

Pang CP, Baum L, Chan WM et al (2000) The apolipoprotein E epsilon4 allele is unlikely to be a major risk factor of age-related macular degeneration in Chinese. Ophthalmologica 214:289–291

Park KH, Fridley BL, Ryu E et al (2009) Complement component 3 (C3) haplotypes and risk of advanced age-related macular degeneration. Invest Ophthalmol Vis Sci 50:3386–3393

Pasutto F, Matsumoto T, Mardin CY et al (2009) Heterozygous NTF4 mutations impairing neurotrophin-4 signaling in patients with primary open-angle glaucoma. Am J Hum Genet 85:447–456

Pasutto F, Chavarria-Soley G, Mardin CY et al (2010) Heterozygous loss-of-function variants in CYP1B1 predispose to primary open-angle glaucoma. Invest Ophthalmol Vis Sci 51:249–254

Peter I, Huggins GS, Ordovas JM et al (2011) Evaluation of new and established age-related macular degeneration susceptibility genes in the women's health initiative sight exam (WHI-SE) study. Am J Ophthalmol 152:1005–1013

Poirier J, Baccichet A, Dea D et al (1993) Cholesterol synthesis and lipoprotein reuptake during synaptic remodelling in hippocampus in adult rats. Neuroscience 55:81–90

Polansky JR, Fauss DJ, Chen P et al (1997) Cellular pharmacology and molecular biology of the trabecular meshwork inducible glucocorticoid response gene product. Ophthalmologica 211:126–139

Pulido JS, Peterson LM, Mutapcic L et al (2007) LOC387715/HTRA1 and complement factor H variants in patients with age-related macular degeneration seen at the mayo clinic. Ophthalmic Genet 28:203–207

Ramdas WD, van Koolwijk LM, Ikram MK et al (2010) A genome-wide association study of optic disc parameters. PLoS Genet. doi:10.1371/journal.pgen.1000978

Ramdas WD, van Koolwijk LM, Lemij HG et al (2011a) Common genetic variants associated with open-angle glaucoma. Hum Mol Genet 20:2464–2471

Ramdas WD, van Koolwijk LM, Cree AJ et al (2011b) Clinical implications of old and new genes for open-angle glaucoma. Ophthalmology 118:2389–2397

Ressiniotis T, Griffiths PG, Birch M et al (2004) The role of apolipoprotein E gene polymorphisms in primary open-angle glaucoma. Arch Ophthalmol 122:258–261

Rezaie T, Child A, Hitchings R et al (2002) Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science 295:1077–1079

Ricci F, Zampatti S, D'Abbruzzi F et al (2009) Typing of ARMS2 and CFH in age-related macular degeneration: case–control study and assessment of frequency in the Italian population. Arch Ophthalmol 127:1368–1372

Richardson AJ, Islam FM, Guymer RH et al (2009) Analysis of rare variants in the complement component 2 (C2) and factor B (BF) genes refine association for age-related macular degeneration (AMD). Invest Ophthalmol Vis Sci 50:540–543

Richardson AJ, Islam FA, Aung KZ et al (2010) Analysis of the chromosome 10q26 region indicates the intergenic region between the tagSNP rs3793917 and rs11200638 in the HTRA1 gene as associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 51:4932–4936

Rivera A, Fisher SA, Fritsche LG et al (2005) Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. Hum Mol Genet 14:3227–3236

Rodriguez de Cordoba S, Esparza-Gordillo J, Goicoechea de Jorge E et al (2004) The human complement factor H: functional roles, genetic variations and disease associations. Mol Immunol 41:355–367

Rontu R, Ojala P, Hervonen A et al (2006) Apolipoprotein E genotype is related to plasma levels of C-reactive protein and lipids and to longevity in nonagenarians. Clin Endocrinol (Oxf) 64:265–270

Ross RJ, Bojanowski CM, Wang JJ et al (2007) The LOC387715 polymorphism and age-related macular degeneration: replication in three case–control samples. Invest Ophthalmol Vis Sci 48:1128–1132

Saglar E, Yucel D, Bozkurt B et al (2009) Association of polymorphisms in APOE, p53, and p21 with primary open-angle glaucoma in Turkish patients. Mol Vis 15:1270–1276

Sahu A, Lambris JD (2001) Structure and biology of complement protein C3, a connecting link between innate and acquired immunity. Immunol Rev 180:35–48

Sarfarazi CA, Stoilova D et al (1998) Localization of the fourth locus (GLC1E) for adult-onset primary open-angle glaucoma to the 10p15-p14 region. Am J Hum Genet 62:641–652

Schaumberg DA, Christen WG, Kozlowski P et al (2006) A prospective assessment of the Y402H variant in complement factor H, genetic variants in C-reactive protein, and risk of age-related macular degeneration. Invest Ophthalmol Vis Sci 47:2336–2340

Schaumberg DA, Hankinson SE, Guo Q et al (2007) A prospective study of 2 major age-related macular degeneration susceptibility alleles and interactions with modifiable risk factors. Arch Ophthalmol 125:55–62

Schmidt S, Saunders AM, De La Paz MA et al (2000) Association of the apolipoprotein E gene with age-related macular degeneration: possible effect modification by family history, age, and gender. Mol Vis 6:287–293

Schmidt S, Klaver C, Saunders A et al (2002) A pooled case–control study of the apolipoprotein E (APOE) gene in age-related maculopathy. Ophthalmic Genet 23:209–223

Schmidt S, Haines JL, Postel EA et al (2005) Joint effects of smoking history and APOE genotypes in age-related macular degeneration. Mol Vis 11:941–949, Am J Hum Genet 78:852–864

Schmidt S, Hauser MA, Scott WK et al (2006) Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. Am J Hum Genet 78(5):852–864

Scholl HP, Fleckenstein M, Fritsche LG et al (2009) CFH, C3 and ARMS2 are significant risk loci for susceptibility but not for disease progression of geographic atrophy due to AMD. PLoS One 4:e7418

Schultz DW, Klein ML, Humpert A et al (2003) Lack of an association of apolipoprotein E gene polymorphisms

with familial age-related macular degeneration. Arch Ophthalmol 121:679–683
Schwartz JT, Reuling FH, Feinleib M (1975) Size of the physiologic cup of the optic nerve head. Arch Ophthalmol 93:776–780
Scott WK, Schmidt S, Hauser MA et al (2007) Independent effects of complement factor H Y402H polymorphism and cigarette smoking on risk of age-related macular degeneration. Ophthalmology 114:1151–1156
Seddon JM, Santangelo SL, Book K et al (2003) A genome-wide scan for age-related macular degeneration provides evidence for linkage to several chromosomal regions. Am J Hum Genet 73:780–790
Seddon JM, George S, Rosner B et al (2006) CFH gene variant, Y402H, and smoking, body mass index, environmental associations with advanced age-related macular degeneration. Hum Hered 61:157–165
Seddon JM, Francis PJ, George S et al (2007) Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. JAMA 297:1793–1800
Seitsonen S, Lemmela S, Holopainen J et al (2006) Analysis of variants in the complement factor H, the elongation of very long chain fatty acids-like 4 and the hemicentin 1 genes of age-related macular degeneration in the Finnish population. Mol Vis 12:796–801
Seitsonen SP, Onkamo P, Peng G et al (2008) Multifactor effects and evidence of potential interaction between complement factor H Y402H and LOC387715 A69S in age-related macular degeneration. PLoS One 3:e3833
Sepp T, Khan JC, Thurlby DA et al (2006) Complement factor H variant Y402H is a major risk determinant for geographic atrophy and choroidal neovascularization in smokers and nonsmokers. Invest Ophthalmol Vis Sci 47:536–540
Sheffield VC, Stone EM, Alward WLM et al (1993) Genetic linkage of familial open angle glaucoma to chromosome 1q21-q31. Nat Genet 4:47–50
Simonelli F, Margaglione M, Testa F et al (2001) Apolipoprotein E polymorphisms in age-related macular degeneration in an Italian population. Ophthalmic Res 33:325–328
Skerka C, Lauer N, Weinberger AA et al (2007) Defective complement control of factor H (Y402H) and FHL-1 in age-related macular degeneration. Mol Immunol 44:3398–3406
Slooter AJ, Tang MX, van Duijn CM et al (1997) Apolipoprotein E epsilon4 and the risk of dementia with stroke. A population-based investigation. JAMA 277:818–821
Souied EH, Benlian P, Amouyel P et al (1998) The epsilon4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration. Am J Ophthalmol 125:353–359
Souied EH, Leveziel N, Richard F et al (2005) Y402H complement factor H polymorphism associated with exudative age-related macular degeneration in the French population. Mol Vis 11:1135–1140
Spencer KL, Hauser MA, Olson LM et al (2007) Protective effect of complement factor B and complement component 2 variants in age-related macular degeneration. Hum Mol Genet 16:1986–1992
Spencer KL, Hauser MA, Olson LM et al (2008a) Deletion of CFHR3 and CFHR1 genes in age-related macular degeneration. Hum Mol Genet 17:971–977
Spencer KL, Olson LM, Anderson BM et al (2008b) C3 R102G polymorphism increases risk of age-related macular degeneration. Hum Mol Genet 17:1821–1824
Stone EM, Fingert JH, Alward WLM et al (1997) Identification of a gene that causes primary open angle glaucoma. Science 275:668–670
Strunnikova NV, Maminishkis A, Barb JJ et al (2010) Transcriptome analysis and molecular signature of human retinal pigment epithelium. Hum Mol Genet 19:2468–2486
Tamura Y, Konomi H, Sawada H et al (1991) Tissue distribution of type VIII collagen in human adult and fetal eyes. Invest Ophthalmol Vis Sci 32:2636–2644
Tang NP, Zhou B, Wang B et al (2009) HTRA1 promoter polymorphism and risk of age-related macular degeneration: a meta-analysis. Ann Epidemiol 19:740–745
Tedeschi-Blok N, Buckley J, Varma R et al (2007) Population-based study of early age-related macular degeneration: role of the complement factor H Y402H polymorphism in bilateral but not unilateral disease. Ophthalmology 114:99–103
Thakkinstian A, Han P, McEvoy M et al (2006) Systematic review and meta-analysis of the association between complementary factor H Y402H polymorphisms and age-related macular degeneration. Hum Mol Genet 15:2784–2790
Thakkinstian A, McKay GJ, McEvoy M et al (2011) Systematic review and meta-analysis of the association between complement component 3 and age-related macular degeneration: a HuGe review and meta-analysis. Am J Epidemiol 173:1365–1379
Thorleifsson G, Walters GB, Hewitt AW et al (2010) Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. Nat Genet 42:906–909
Tielsch JM, Katz J, Sommer A et al (1994) Family history and risk of primary open angle glaucoma. Arch Ophthalmol 112:69–73
Tikellis G, Sun C, Gorin MB et al (2007) Apolipoprotein E gene and age-related maculopathy in older individuals: the cardiovascular health study. Arch Ophthalmol 125:68–73
Tong Y, Liao J, Zhang Y et al (2010) LOC3877015/HTRA1 gene polymorphisms and susceptibility to age-related macular degeneration: a HuGe review and meta-analysis. Mol Vis 16:1958–1981
Tsai FJ, Lin HJ, Chen WC et al (2003) Insulin-like growth factor-II gene polymorphism is associated with primary open angle glaucoma. J Clin Lab Anal 17:259–263
Tserentsoodol N, Gordiyenko NV, Pascual I et al (2006) Intraretinal lipid transport is dependent on high density lipoprotein-like particles and class B scavenger receptors. Mol Vis 12:1319–1333
Tunny TJ, Richardson KA, Clark CV et al (1996) The atrial natriuretic peptide gene in patients with familial

primary open-angle glaucoma. Biochem Biophys Res Commun 223:221–225
Tuo J, Ross RJ, Reed GF et al (2008) The HtrA1 promoter polymorphism, smoking, and age-related macular degeneration in multiple case–control samples. Ophthalmology 11:1891–1898
Utheim OA, Ritland JS, Utheim TP et al (2008) Apolipoprotein E genotype and risk for development of cataract and age-related macular degeneration. Acta Ophthalmol 86:401–403
van Koolwijk LME, Despriet DDG, van Duijn CM et al (2007) Genetic contributions to glaucoma: heritability of intraocular pressure, retinal nerve fiber layer thickness, and optic disc morphology. Invest Ophthalmol Vis Sci 48:3669–3676
van Koolwijk LME, Ramdas WD, Ikram MK et al (2012) Common genetic determinants of intraocular pressure and primary open-angle glaucoma. PLoS Genet 8(5):e1002611
Vickers JC, Craig JE, Stankovich J et al (2002) The apolipoprotein ε4 gene is associated with elevated risk of normal tension glaucoma. Mol Vis 14:389–393
Vithana EN, Nongpiur ME, Venkataraman D et al (2010) Identification of a novel mutation in the NTF4 gene that causes primary open-angle glaucoma in a Chinese population. Mol Vis 16:1640–1645
von Graefe A (1869) Beitrage zur Pathologie und Therapie des Glaukoms. Arch Ophthalmol 15:108–252
Wang CY, Shen YC, Lo FY et al (2006) Polymorphism in the IL-1alpha (-889) locus associated with elevated risk of primary open angle glaucoma. Mol Vis 12: 1380–1385
Wang W, Connor SL, Johnson EJ et al (2007) Effect of dietary lutein and zeaxanthin on plasma carotenoids and their transport in lipoproteins in age-related macular degeneration. Am J Clin Nutr 85:762–769
Wang AL, Lukas TJ, Yuan M et al (2008a) Increased mitochondrial DNA damage and down-regulation of DNA repair enzymes in aged rodent retinal pigment epithelium and choroid. Mol Vis 14:644–651
Wang J, Ohno-Matsui K, Yoshida T et al (2008b) Altered function of factor I caused by amyloid beta: implication for pathogenesis of age-related macular degeneration from Drusen. J Immunol 181:712–720
Wang JJ, Ross RJ, Tuo J et al (2008c) The LOC387715 polymorphism, inflammatory markers, smoking, and age-related macular degeneration. A population-based case control study. Ophthalmology 115:693–699
Wang G, Spencer KL, Court BL et al (2009a) Localization of age-related macular degeneration-associated ARMS2 in cytosol, not mitochondria. Invest Ophthalmol Vis Sci 50:3084–3090
Wang JJ, Rochtchina E, Smith W et al (2009b) Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. Am J Epidemiol 169:633–641
Wang G, Spencer KL, Scott WK et al (2010a) Analysis of the indel at the ARMS2 3'UTR in age-related macular degeneration. Hum Genet 127(5):595–602
Wang L, Clark ME, Crossman DK et al (2010b) Abundant lipid and protein components of drusen. PLoS One 5:e10329
Weber BH, Vogt G, Pruett RC et al (1994) Mutations in the tissue inhibitor of metalloproteinases-3 (TIMP3) in patients with Sorsby's fundus dystrophy. Nat Genet 8:352–356
Weeks DE, Conley YP, Tsai HJ et al (2004) Age-related maculopathy: a genome-wide scan with continued evidence of susceptibility loci within the 1q31, 10q26, and 17q25 regions. Am J Hum Genet 75:174–189
Weger M, Renner W, Steinbrugger I et al (2007) Association of the HTRA1-625G>A promoter gene polymorphism with exudative age-related macular degeneration in a Central European population. Mol Vis 13:1274–1279
Wegscheider BJ, Weger M, Renner W et al (2007) Association of complement factor H Y402H gene polymorphism with different subtypes of exudative age-related macular degeneration. Ophthalmology 114: 738–742
Willer CJ, Sanna S, Jackson AU et al (2008) Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nat Genet 40: 161–169
Wolfs RC, Klaver CCW, Ramrattan RS et al (1998) Genetic risk of primary open-angle glaucoma. Population-based aggregation study. Arch Ophthalmol 116:1640–1645
Wong TY, Shankar A, Klein R et al (2006) Apolipoprotein E gene and early age-related maculopathy: the Atherosclerosis Risk in Communities Study. Ophthalmology 113:255–259
Xu Y, Guan N, Xu J et al (2008) Association of CFH, LOC387715, and HTRA1 polymorphisms with exudative age-related macular degeneration in a northern Chinese population. Mol Vis 14:1373–1381
Yang Z, Camp NJ, Sun H et al (2006) A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science 314:992–993
Yang Z, Tong Z, Chen Y et al (2010) Genetic and functional dissection of HTRA1 and LOC387715 in age-related macular degeneration. PLoS Genet 6(2):e1000836
Yates JR, Sepp T, Matharu BK et al (2007) Complement C3 variant and the risk of age-related macular degeneration. N Engl J Med 357:553–561
Yoshida T, DeWan A, Zhang H et al (2007) HTRA1 promoter polymorphism predisposes Japanese to age-related macular degeneration. Mol Vis 13:545–548
Yu Y, Bhangale TR, Fagerness J et al (2011a) Common variants near FRK/COL10A1 and VEGFA are associated with advanced age-related macular degeneration. Hum Mol Genet 20:3699–3709
Yu Y, Reynolds R, Fagerness J et al (2011b) Association of variants in the LIPC and ABCA1 genes with intermediate and large drusen and advanced age-related macular degeneration. Invest Ophthalmol Vis Sci 52:4463–4670
Zannis VI (1986) Genetic polymorphism in human apolipoprotein E. Methods Enzymol 128:823–851

Zareparsi S, Reddick AC, Branham KE et al (2004) Association of apolipoprotein E alleles with susceptibility to age-related macular degeneration in a large cohort from a single center. Invest Ophthalmol Vis Sci 45:1306–1310

Zareparsi S, Branham KE, Li M et al (2005) Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. Am J Hum Genet 77:149–153

Ziskind A, Bardien S, van der Merwe L et al (2008) The frequency of the H402 allele of CFH and its involvement with age-related maculopathy in an aged Black African Xhosa population. Ophthalmic Genet 29: 117–119

Zumbrunn J, Trueb B (1996) Primary structure of a putative serine protease specific for IGF-binding proteins. FEBS Lett 398:187–192

# 6 Preventive Therapies for Age-Related Macular Degeneration: Current Guidelines

Naima Jacobs-El, Catherine Meyerle, and Emily Y. Chew

## 6.1 Introduction

While cataract and glaucoma are the most common causes of blindness among blacks, age-related macular degeneration (AMD) is the leading cause in whites in the USA (Congdon et al. 2004). Although no evidence-based nutritional recommendations exist in the management of glaucoma or age-related cataracts (Age-Related Eye Disease Study Research Group 2001a), research has supported nutritional treatment strategies for AMD. This chapter will focus on nutritional therapy for AMD.

The pathophysiology of AMD, though not well understood, may be multifactorial with contributions potentially from oxidative damage (Fliesler and Anderson 1983; Gerster 1991; Beatty et al. 2000), genetic factors, and immunologic processes (Tuo et al. 2012). Retinal tissue is exceedingly sensitive to oxidative damage due to its high rate of metabolic activity and frequent exposure to light. Oxidative damage may play a central role in the development of AMD. Consequently, there is great interest in determining modifiable environmental and dietary factors to prevent development and progression of AMD.

The current data regarding micronutrient effects on AMD comes from both large observational studies and a small number of randomized controlled trials. In some instances, the findings of these studies are inconsistent. In evaluating the findings of the available nutritional studies, the Cochrane review (Evans 2006) concluded that the existing evidence regarding micronutrient supplementation in retarding the progression of AMD is derived mainly from the Age-Related Eye Disease Study (AREDS). These nutrients include beta-carotene, vitamins C and E, B vitamins, zinc, omega-3 fatty acids, and macular xanthophylls (lutein and zeaxanthin) (Coleman and Chew 2007; Evans 2006; Evans and Henshaw 2000, 2008; Johnson 2010).

The Age-Related Eye Disease Study 2 (AREDS2) is currently under way to test the role of lutein/zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids in preventing the development of advanced AMD in patients at an intermediate or high risk of progression. Because of the increased risk of lung cancer in smokers who take beta-carotene, AREDS 2 will evaluate the effects of elimination of beta-carotene. The optimal dose of zinc in the AREDS formulation will also be tested by decreasing the current dose.

## 6.2 Observational Studies

A number of observational studies suggest an important association between dietary intake and AMD. These include the Rotterdam Study, Blue

N. Jacobs-El, MD • C. Meyerle, MD • E.Y. Chew, MD (✉)
Division of Epidemiology and Clinical Applications, Clinical Trials Branch, National Eye Institute NIH, Building 10, CRC, Room 3-2531, 10 Center Drive, MSC 1204, Bethesda, MD 20892, USA
e-mail: echew@nei.nih.gov

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_6, © Springer-Verlag Berlin Heidelberg 2013

Mountains Eye Study, the Beaver Dam Eye Study, the Carotenoids in Age-Related Macular Degeneration Study, the Nurses' Health Study, and Health Professionals Follow-Up Study.

### 6.2.1 Rotterdam Study

The Rotterdam Study was a population-based, prospective cohort study of 4,170 participants living in the Netherlands aged 55 years or older with no AMD in either eye at the baseline of the study. Dietary intake was assessed at baseline using a semiquantitative food frequency questionnaire, and incident AMD was determined by evaluation of fundus photographs by a grading center. Incident AMD was defined as soft distinct drusen with pigment alterations, indistinct or reticular drusen, geographic atrophy, or choroidal neovascularization. After a mean follow-up of 8 years, an above-median intake of beta-carotene, vitamin C, vitamin E, and zinc was associated with a 35 % reduced risk (HR, 0.65; 95 % CI, 0.46–0.92) of AMD (van Leeuwen et al. 2005).

### 6.2.2 Blue Mountains Eye Study

The Blue Mountains Eye Study, another population-based cohort study, included 2,335 subjects aged 49 and older. Dietary intake, derived from a standardized questionnaire, was analyzed for an association with incident AMD over a 10-year study period. Beta-carotene was found to be a risk factor for the development of incident neovascular AMD (relative risk (RR) of 2.4 when comparing top tertile of intake with bottom tertile) (Tan et al. 2008).

In contrast, the Blue Mountains Eye participants with the highest intake of lutein/zeaxanthin had a reduced risk of incident neovascular AMD (RR, 0.35). Furthermore, those subjects with above-median intakes of lutein/zeaxanthin had a reduced risk of indistinct soft or reticular drusen (RR, 0.66) (Tan et al. 2009). The participants with the highest tertile of zinc intake were 46 % less likely to develop early AMD and 44 % less likely to develop any AMD (Tan et al. 2008).

### 6.2.3 The Beaver Dam Eye Study

The Beaver Dam Eye Study evaluated 1,709 Wisconsin participants aged 43–84. Dietary information was gathered using a food frequency questionnaire and incident AMD determined using masked grading of stereoscopic color fundus photographs. After 5 years of follow-up, there were significant inverse associations ($P<0.05$) between intakes of provitamin A carotenoids and dietary vitamin E and the incidence of large drusen. It also showed a significant inverse association between zinc and the incidence of pigmentary abnormalities. No significant inverse associations were found between antioxidant or zinc intake and the incidence of overall early ARM. However, because there were too few incident late ARM cases in this cohort, the study was unable to assess whether antioxidant intake was associated with the progression of early AMD to late stage AMD (VandenLangenberg et al. 1998).

### 6.2.4 Carotenoids in Age-Related Macular Degeneration Study

The Carotenoids in Age-Related Macular Degeneration Study (CAREDS) evaluated 1,787 females aged 50–79 years in the USA with intake of lutein/zeaxanthin above the 78th (high) and below the 28th (low) percentiles. These participants were enrolled 4–7 years from the baseline of the study between 1994 and 1998. CAREDS found that the prevalence of intermediate AMD was not statistically different between the high- and low-lutein/zeaxanthin-intake groups after adjusting for age (odds ratio, 0.96; 95 % confidence interval, 0.75–1.23). However, in an analysis of women participants younger than 75 years, a substantially lowered odds ratios was seen (0.57; 95 % confidence interval, 0.34–0.95) (Moeller et al. 2006).

### 6.2.5 Nurses' Health Study and Health Professionals Follow-Up Study

The Nurses' Health Study and Health Professionals Follow-Up Study in the USA involved a large

prospective follow-up evaluation of 71,494 women and 41,564 men aged 50 and older without AMD at baseline. During the study period, up to 18 years for women and 16 years for men, there was a statistically nonsignificant reduction in self-reported incident neovascular AMD with increased consumption of lutein/zeaxanthin (Cho et al. 2008). Lutein/zeaxanthin intake was not associated with the risk of self-reported early AMD.

## 6.3 Randomized Controlled Trials

The randomized controlled trials evaluating the impact of nutritional supplements on AMD are few in number. These include the vitamin E, cataract, and age-related maculopathy trial (VECAT), Physicians' Health Study, and the Age-Related Eye Disease Study.

### 6.3.1 Vitamin E, Cataract, and Age-Related Maculopathy Trial

The VECAT, a prospective randomized placebo-controlled trial, evaluated the effect of vitamin E 500 international units (IU) on the incidence of AMD in an urban Australian population. The study included 1,193 participants who were enrolled between 1995 and 1996. After the 4-year study period, there was no effect of vitamin E supplementation on the incidence of early or late AMD (Taylor et al. 2002).

### 6.3.2 Physicians' Health Study

The Physicians' Health Study, a randomized double-masked controlled trial of beta-carotene, involved 21,120 US male physician participants with no AMD at baseline in 1982. This study also included an observational arm wherein subjects reported their patterns of consumption of vitamin C and vitamin E on a dietary questionnaire. During the 12.5 average years of follow-up, beta-carotene was not found to have a significant effect on progression of AMD (Chiu et al. 2009; Christen et al. 2007). Those subjects taking vitamin E supplements had a 13 % reduced risk of self-reported AMD (RR = 0.87) (Christen et al. 1999) and users of vitamin C supplements had a relative risk of 1.03 (95 % Cl 0.71–1.50) for AMD; neither one was statistically significant.

Data from two large randomized controlled clinical trials of beta-carotene demonstrated an increased lung cancer risk with beta-carotene supplementation in smokers (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994; Omenn et al. 1996), using 20–30 mg beta-carotene. Contrary to these studies, the Physicians' Health Study did not show a significant difference in lung cancer risk or overall mortality in the randomized controlled clinical trial (Hennekens et al. 1996).

### 6.3.3 Oral Zinc in Macular Degeneration

Newsome et al. conducted a prospective, randomized, double-masked, placebo-controlled pilot study of oral zinc in 151 subjects with drusen or macular degeneration. When comparing fundus photos from the final study visit with baseline photos, significantly more eyes in the zinc-treated group either remained stable or showed less accumulation of drusen. Furthermore, the zinc-treated group had significantly less visual loss than the placebo group after a follow-up of 12–24 months (Newsome et al. 1988). The placebo group of participants had an unusually high rate of vision loss in this study; the proportion of loss of 20 or more letters of visual acuity was 2.5 times less in the zinc-treated group than the placebo group.

### 6.3.4 Age-Related Eye Disease Study

The Age-Related Eye Disease Study (AREDS) was a long-term, multicenter, prospective study of the clinical course and prognosis of AMD and age-related cataract. The study included 4,757 participants, aged 55–80 years, enrolled between 1992 and 1998. In addition to collecting natural

**Table 6.1** AREDS Formulation: Daily Dose

| |
|---|
| Vitamin C 500 mg |
| Vitamin E 400 IU |
| Beta-carotene 15 mg |
| Zinc 80 mg |
| Copper 2 mg |

history data, AREDS included a 5-year clinical trial of moderate- to high-dose vitamin and mineral supplements to examine the effect on the progression of AMD (Age-Related Eye Disease Study Research Group 1999). 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 AREDS showed that the supplementation of antioxidants plus zinc reduced the risk of progression to advanced AMD by approximately 25 % in participants with AREDS categories 3 and 4 (odds ratio [OR], 0.72; 99 % confidence interval [CI], 0.52–0.98) (Age-Related Eye Disease Study Research Group 2001b). These categories are defined by extensive intermediate drusen, large drusen, and noncentral geographic atrophy in one or both eyes (category 3) or advanced AMD or visual acuity <20/32 attributable to AMD in one eye (category 4).

In AREDS, the clinical importance of the reduction in the development of advanced AMD was corroborated by the accompanying effect on visual acuity. Compared with the placebo group, the participants in categories 3 and 4 assigned to antioxidants plus zinc had a statistically significant estimated 27 % reduction in the odds of a 15-letter or greater visual acuity decrease ($P = .008$). Thus, the AREDS concluded that patients with extensive intermediate size drusen, at least one large druse, noncentral geographic atrophy in one or both eyes, or advanced AMD or vision loss due to AMD in one eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as an AREDS-type supplement (Table 6.1) (Age-Related Eye Disease Study Research Group 2001b).

There were minimal adverse outcomes during the AREDS study. During the study period, there was no statistically significant difference between treatment arms in use of lipid-lowering medications at 5 years after enrollment (Age-Related Eye Disease Study Research Group 2001b). However, participants in the antioxidant arms more frequently reported yellow skin (8.3 % vs. 6.0 %; $P = .008$). Interestingly, participants in the zinc arms showed an excess of self-reported anemia (13.2 % vs. 10.2 %; $P = .004$), but serum hematocrit levels showed no difference (Age-Related Eye Disease Study Research Group 2001b). Furthermore, no clinically or statistically significant difference from baseline in serum levels of cholesterol or hematocrit was observed during the 5-year period (Age-Related Eye Disease Study Research Group 2001b). There were, however, higher rates of hospitalization for genitourinary conditions in patients randomized to the zinc arm of the study compared to those who were not on zinc formulations (7.5 % vs. 4.9 % for both men and women and 8.6 % vs. 4.4 % for men alone) (Age-Related Eye Disease Study Research Group 2001b). These genitourinary conditions included unspecified urinary tract infection, prostatic hyperplasia in men, and stress incontinence in women.

Interestingly, participants taking zinc supplements, either alone or in combination with other antioxidants, had decreased mortality in the AREDS than those not taking zinc (RR 0.78; 95 % CI, 0.41–1.47) (Clemons et al. 2004). AREDS analyses did not show any increased risk of mortality with AREDS supplementation (Clemons et al. 2004). However, a large meta-analysis of controlled clinical trials examining the impact of vitamin E on mortality showed a minimally increased risk of mortality with vitamin E supplementation both when used alone and in combination with beta-carotene and vitamin A (RR 1.04) (Bjelakovic et al. 2007). The AREDS data suggests that patients homozygous for the risk conferring phenotype of complement factor H (Y402H/Y402H) have a reduced treatment response to zinc (Klein et al. 2008).

The observational data from AREDS found that dietary total omega-3 long-chain polyunsaturated

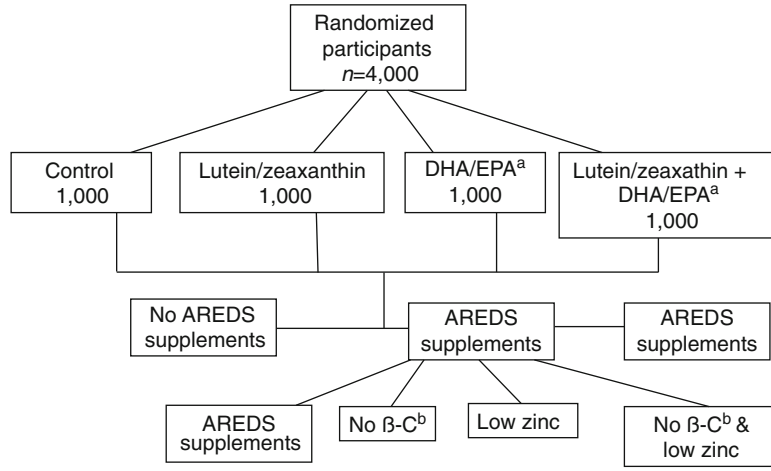


**Fig. 6.1** Age-related eye disease study 2 (AREDS2) study design. *a* docosahexaenoic acid and eicosapentaenoic acid, *b* Beta-carotene

fatty acid (LCPUFA) intake was inversely associated with neovascular AMD (odds ratio [OR], 0.61; 95 % confidence interval [CI], 0.41–0.90). Docosahexaenoic acid, an omega-3 LCPUFA which is an important structural component in membranes in the retina, was also associated with decreased risk of neovascular AMD (OR, 0.54; 95 % CI, 0.36–0.80). Higher fish consumption, both total and broiled/baked, was also inversely associated with NV AMD (OR, 0.61; 95 % CI, 0.37–1.00 and OR, 0.65; 95 % CI, 0.45–0.93, respectively). Similarly, when comparing the highest and lowest quintiles of intake in the AREDS population, lutein and zeaxanthin intake was independently inversely associated with NV AMD (OR 0.65), geographic atrophy (OR, 0.45), and large or extensive intermediate drusen (OR, 0.73) (SanGiovanni et al. 2007).

### 6.3.5 Age-Related Eye Disease Study 2

In addition to the observational data from AREDS, other epidemiologic studies have suggested a possible protective effect of lutein/zeaxanthin and omega-3 fatty acids for advanced AMD. The data are compelling to conduct a large clinical trial to test the roles of these two nutrients. The Age-Related Eye Disease Study 2 (AREDS2) was designed to address these hypotheses.

The AREDS2 is a multicenter, placebo-controlled, randomized trial with the primary purpose of evaluating the efficacy and safety of lutein and zeaxanthin and/or omega-3 LCPUFA supplementation in reducing the risk of developing advanced AMD. Secondarily, the study will evaluate the elimination of beta-carotene (The AREDS2 Research Group 2012; Coleman and Chew 2007) as well as a lower dose of zinc (as compared to AREDS) in reducing the risk of developing advanced AMD.

In contrast to AREDS, AREDS2 included only participants at intermediate risk, or higher, of progression to AMD. Approximately 4,000 patients have been enrolled who have either (1) bilateral large drusen or (2) large drusen in one eye and advanced AMD (NV AMD or central geographic atrophy) in the fellow eye. The primary outcome measure in AREDS2 is progression to advanced AMD during the 5-year study period (Fig. 6.1).

In the primary randomization, study participants were randomly assigned to take one of the following treatment arms: (1) placebo (AREDS formulation), (2) lutein 10 mg and zeaxanthin 2 mg, (3) DHA 350 mg and EPA 650 mg, or (4) lutein 10 mg and zeaxanthin 2 mg and DHA 350 mg and EPA 650 mg.

All participants other than the placebo group were offered the choice of AREDS formulation or a second randomization to receive one of four alternative AREDS formulations (Table 6.2). Consequently, the AREDS2 trial will provide further evidence on the refinement of the ARED-type supplement in addition to its primary outcome.

**Table 6.2** Four alternative AREDS formulations being tested in the secondary randomization of AREDS2

| Formulations | Vitamin C (mg) | Vitamin E (IU) | Beta-carotene (mg) | Zinc oxide (mg) | Cupric oxide (mg) |
|---|---|---|---|---|---|
| 1 | 500 | 400 | 15 | 80 | 2 |
| 2 | 500 | 400 | 0 | 80 | 2 |
| 3 | 500 | 400 | 15 | 25 | 2 |
| 4 | 500 | 400 | 0 | 25 | 2 |

## 6.4 Recommendations

Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Based on current literature, persons found to have intermediate or high-risk AMD (extensive intermediate size drusen, at least one large druse, noncentral geographic atrophy in one or both eyes, or advanced AMD or vision loss due to AMD in one eye) should be considered for micronutrient supplementation. If such patients are without contraindications such as smoking, the treating physician may consider recommending AREDS-type supplements (Age-Related Eye Disease Study Research Group 2001b). If such patients are smokers or recent former smokers, the treating physician may consider recommending AREDS-type supplementation that excludes the beta-carotene component; the patient should also be advised to quit smoking. No evidence-based recommendations exist for nutritional supplementation in patients with early AMD. Similarly, neither the AREDS nor the several documented observational studies evaluated bilateral advanced AMD; thus, no evidence-based recommendations exist for nutritional supplementation in patients with advanced AMD findings.

### Conclusion

While there is strong evidence for supplementation for intermediate or high-risk AMD, there is currently insufficient data regarding nutritional supplementation for patients with early or bilateral advanced AMD. Additionally, there is insufficient evidence in the literature to recommend routine nutritional supplementation in healthy adults for primary prevention of AMD. Intermediate- to high-risk AMD patients may consider taking AREDS-type supplements as appropriate given their overall health status. Observational studies have also suggested benefit from increased dietary intake of macular xanthophylls and omega-3 fatty acids and lowering carbohydrate intake. The currently underway large randomized controlled trial AREDS2 will help elucidate the role of lutein/zeaxanthin and omega-3 LPPUFAs in the management of AMD. Developing effective preventive therapies for AMD, which is an increasing public health problem, is essential for future research efforts.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Age-Related Eye Disease Study Research Group (1999) The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. Control Clin Trials 20:573–600

Age-Related Eye Disease Study Research Group (2001a) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 119:1439–1452

Age-Related Eye Disease Study Research Group (2001b) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 119:1417–1436

Beatty S, Koh H, Phil M, Henson D, Boulton M (2000) The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 45: 115–134

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C (2007) Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 297:842–857

Chiu CJ, Milton RC, Klein R, Gensler G, Taylor A (2009) Dietary compound score and risk of age-related macular degeneration in the age-related eye disease study. Ophthalmology 116:939–946

Cho E, Hankinson SE, Rosner B, Willett WC, Colditz GA (2008) Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. Am J Clin Nutr 87:1837–1843

Christen WG, Ajani UA, Glynn RJ, Manson JE, Schaumberg DA, Chew EC, Buring JE, Hennekens CH (1999) Prospective cohort study of antioxidant vitamin supplement use and the risk of age-related maculopathy. Am J Epidemiol 149:476–484

Christen WG, Manson JE, Glynn RJ, Gaziano JM, Chew EY, Buring JE, Hennekens CH (2007) Beta carotene supplementation and age-related maculopathy in a randomized trial of US physicians. Arch Ophthalmol 125:333–339

Clemons TE, Kurinij N, Sperduto RD (2004) Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS report no. 13. Arch Ophthalmol 122:716–726

Coleman H, Chew E (2007) Nutritional supplementation in age-related macular degeneration. Curr Opin Ophthalmol 18:220–223

Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P (2004) Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 122: 477–485

Evans JR (2006) Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev:CD000254

Evans JR, Henshaw K (2000) Antioxidant vitamin and mineral supplementation for preventing age-related macular degeneration. Cochrane Database Syst Rev:CD000253

Evans JR, Henshaw K (2008) Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database Syst Rev:CD000253

Fliesler SJ, Anderson RE (1983) Chemistry and metabolism of lipids in the vertebrate retina. Prog Lipid Res 22:79–131

Gerster H (1991) Review: antioxidant protection of the ageing macula. Age Ageing 20:60–69

Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R (1996) Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 334:1145–1149

Johnson EJ (2010) Age-related macular degeneration and antioxidant vitamins: recent findings. Curr Opin Clin Nutr Metab Care 13:28–33

Klein ML, Francis PJ, Rosner B, Reynolds R, Hamon SC, Schultz DW, Ott J, Seddon JM (2008) CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. Ophthalmology 115:1019–1025

Moeller SM, Parekh N, Tinker L, Ritenbaugh C, Blodi B, Wallace RB, Mares JA (2006) Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-related Eye Disease Study (CAREDS): ancillary study of the Women's Health Initiative. Arch Ophthalmol 124:1151–1162

Newsome DA, Swartz M, Leone NC, Elston RC, Miller E (1988) Oral zinc in macular degeneration. Arch Ophthalmol 106:192–198

Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S (1996) Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334:1150–1155

SanGiovanni JP, Chew EY, Clemons TE, Davis MD, Ferris FL 3rd, Gensler GR, Kurinij N, Lindblad AS, Milton RC, Seddon JM, Sperduto RD (2007) The relationship of dietary lipid intake and age-related macular degeneration in a case–control study: AREDS report no. 20. Arch Ophthalmol 125:671–679

Tan JS, Wang JJ, Flood V, Rochtchina E, Smith W, Mitchell P (2008) Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 115:334–341

Tan JS, Wang JJ, Flood V, Mitchell P (2009) Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol 127:656–665

Taylor HR, Tikellis G, Robman LD, McCarty CA, McNeil JJ (2002) Vitamin E supplementation and macular degeneration: randomised controlled trial. BMJ 325:11

The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 330:1029–1035

The AREDS2 Research Group (2012) The Age-related Eye Disease Study 2 (AREDS2): Study Design and Baseline Characteristics (AREDS2 Report Number 1). Ophthalmology 119:2282–2289

Tuo J, Grob S, Zhang K, Chan CC (2012) Genetics of immunological and inflammatory components in age-related macular degeneration. Ocul Immunol Inflamm 20:27–36

van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JC, Klaver CC, Hofman A, de Jong PT (2005) Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 294:3101–3107

VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BE, Brady WE, Palta M (1998) Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 148:204–214

# Part III

# Current Treatment of the Major Eye Diseases of the Elderly

# Innovations in Cataract Surgery

7

Oliver K. Klaproth, Marko Ostovic,
and Thomas Kohnen

## 7.1 Introduction

Cataract surgery has come a long way, from couching as long as 5,000 years ago to femtosecond laser lens fragmentation today. Although it is a routine surgery in the Western world today, cataract is still a major cause of blindness in the world, as the availability of surgery in other countries is much worse. And even if cataract surgery is available, posterior YAG capsulotomies might be not. Besides these problems, the development of cataract surgery in the Western world is progressing with huge steps. Smaller incisions, less invasive surgical techniques, and last but not least more precise IOL calculations lead the way to premium IOL. Bi- and trifocal lenses, requiring precise and predictable positioning are being implanted successfully today, due to these developments allowing patients to be independent of their glasses after cataract surgery. This step – from the removal of the blurred lens only towards the aiming for postoperative spectacle independency – marked the change from cataract surgery to refractive cataract surgery, which will be the cataract surgery of the twenty-first century.

O.K. Klaproth, Dipl.-Ing.(FH) • M. Ostovic, MD
T. Kohnen, MD, PhD, FEBO (✉)
Department of Ophthalmology,
Goethe-University, Theodor-Stern-Kai 7,
Frankfurt am Main 60590, Germany
e-mail: o.klaproth@med.uni-frankfurt.de;
marko.ostovic@kgu.de; kohnen@em.uni-frankfurt.de

## 7.2 Cataract

Cataract is, with exception of some special occurrences like traumatic or congenital cataract, age related. Every person who reaches the respective age will suffer from cataract, usually in both eyes. The respective age however depends on many factors, genetic ones as well as such set by environmental conditions like UV exposure or malnutrition. The age-related blurring of the natural lens is still the most common reason for blindness, particularly as in developing countries access to primary cataract surgery and/or treatment of posterior capsule opacification (PCO) is limited. Age-related cataract is responsible for 48 % of world blindness, which represents about 18 million people. Furthermore, lifetime expectation in the Western world is as high as never before; at the same time, the cataract surgery rate (CSR) in new emerging industrial countries increases dramatically (e.g., in India). Cataract surgery has thus become the most often performed surgery worldwide, with estimated 18–20 million surgeries per year, tendency increasing. The impact of an aging society on global CSR is obvious (Kohnen et al. 2009a; WHO 2011). Cataract surgery has become a serious challenge for global health systems – and also a most significant market.

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_7, 

## 7.3 Evolution of Cataract Surgery

Cataract surgery as we know it today is the removal of the crystalline lens using ultrasonic phacoemulsification via a clear corneal or limbal incision and an anterior capsulotomy with the following implantation of an artificial lens in the capsular bag. This procedure has mainly been affected by four surgeons: Sir Harold Ridley, who performed the first intraocular lens implantation in 1949 (Ridley 1952); Charles Kelman, who for the first time introduced ultrasonic phacoemulsification in 1967 (Kelman 1967); and Thomas Neuhann and Howard Gimbel, who proposed the anterior capsulotomy in 1981 and 1985 (Haefliger and Neuhann 1988). Since then improvements have been made in incision sizing (Sect. 7.4.4.1) as well as lens edge design, optic design (Sect. 7.4.2), and IOL calculation (Sect. 7.4.3) to provide a lower rate of posterior capsule opacification and better postoperative quality of vision. Cataract surgery today is more and more seen as refractive surgery (Sect. 7.4.1). The next step on this road might be femtosecond laser phacoemulsification and thus the abandonment of ultrasound exposure resulting in more gentle surgery, even more precise incisions and capsulotomies, less complications like capsular ruptures, as well as more precise and predictable visual results (Sect. 7.4.4.2).

## 7.4 Refractive Cataract Surgery

While the focus in cataract surgery in emerging economies or developing countries lies mostly on increasing accessibility of both primary cataract surgery and treatment of PCO, these are not an issue in the Western world. Since the removal of the blurred lens is a routine standard treatment at the beginning of the twenty-first century, patients as well as surgeons focus more and more on the refractive aspects of cataract surgery (Koch and Kohnen 1999). The aim will be to provide individualized refractive solutions to achieve not only the removal of the blurred lens but also optimized postoperative spectacle independency and comfortable quality of vision (Sect. 7.4.1) at all required distances. Prevention of PCO might be named an issue, but rather for reasons of increased patient comfort than prevention of blindness, as the access to YAG lasers is largely available.

### 7.4.1 Quality of Vision

#### 7.4.1.1 Standard Parameters for Evaluation of Vision

As mentioned above, the major goal of cataract surgery is the replacement of the opacified lens. Thanks to development in biometry (i.e., partial coherence interferometry), today's surgeons are able to achieve postoperative emmetropia (according to the SE, not to astigmatism) with standard spherical lenses in many patients. The standard criteria to evaluate the visual outcome after cataract surgery are safety, predictability, efficacy, and stability of both refraction and visual acuity (Kohnen 2009; Dupps et al. 2011).

#### 7.4.1.2 What Is Quality of Vision?

Quality of vision is a subjective multivariate construct. Based on the assumption that vision in everyday life requires more than just sufficient visual acuity (representing spatial resolution ability of the visual system only), different metrics in four levels of visual perception (anatomy, optics, function, and subjective perception) can be defined. Thus, the individual patient's vision can be quantified more precise. These metrics are, among others, noticeable problems of the anterior segment and topographic metrics (anatomy), refraction, again topography and aberrometry (optics), contrast sensitivity, low- and high-contrast visual acuity (function), and last but not least the assessment of subjective satisfaction by questionnaires (subjective perception). Vision after cataract surgery is more and more judged by these metrics. As a result, different types of more or less individualized IOL have been developed during the past decades, aiming for more convenient visual perception after cataract surgery.

### 7.4.2 Intraocular Lenses (IOL)

Standard monofocal spherical intraocular lenses are designed to correct postcataract aphakia and at the same time the preoperative spherical equivalent

of preoperative ametropia. They are capable of providing neither astigmatism – or higher-order aberration correction – nor near and distance vision at the same time. In many cases these lenses thus cannot provide spectacle independency, no matter how precise preoperative calculation (Sect. 7.4.3) was performed, unless additional surgical procedures are applied, such as incisional techniques or keratorefractive excimer surgery. Several different optics of IOL have been introduced in the past; the main principles include aspheric IOL, toric IOL, multifocal IOL, and "accommodative" IOL as well as combinations of these.

#### 7.4.2.1 Aspheric IOL

While corneal spherical aberration (SA) remains constant, lenticular SA changes from negative values in the juvenile eye towards positive values in older patients adding up to a positive total ocular SA (Wang et al. 2003, 2005). Aspheric IOL (AIOL) are designed to modify the ocular SA after cataract surgery, either by adding no new lenticular SA ("aberration-free IOL") or by compensating for the corneal SA by adding negative lenticular SA (Kohnen and Klaproth 2008). The result is an improvement in quality of vision, namely, retinal image quality, contrast sensitivity, and to a somewhat lower extent visual acuity. However, this theory has two major limitations: pupil size and surgically induced corneal aberrations. AIOL only achieve these positive results for pupil sizes larger than approximately 4–5 mm (Kohnen et al. 2009b). As pupil size shows age-related overall decrease, many cataract patients do not reach this pupil size (Kollarits et al. 1982). The second limitation is due to the surgery itself. The clear corneal incisions, most commonly used for cataract surgery today, induce, depending on size and location, a change in corneal aberrations. Only incisions of approx. 2.2–2.5 mm or smaller are more or less neutral to higher-order aberrations. Thus, only few patients will significantly benefit from the implantation of an AIOL: namely, young patients with large pupils (Kohnen et al. 2009b). AIOL can also be combined with toricity or multifocality.

#### 7.4.2.2 Toric IOL

If one considers the refractive outcome after cataract surgery as a major topic, we have to look at the correction of preexisting astigmatism as a major task. The correction of spherical errors, namely, the correction of the spherical equivalent of ocular aberrations, is today's standard in cataract surgery. Astigmatism, however, as one major source of limited postoperative visual acuity and quality of vision, is only beginning to be addressed in an appropriate way. Options are procedures to modify corneal curvature itself, as limbal relaxing incisions, opposite clear corneal incisions, or additional corneal excimer laser surgery, as well as procedures, that compensate for corneal astigmatism, such as pseudophakic supplementary or primary implanted toric intraocular lenses. The latter ones require a precise predictability of postoperative corneal astigmatism, which can, for example, be achieved by micro-incisional cataract surgery (see Sect. 7.4.4.2).

Toric IOL compensate for the corneal astigmatism (in ideal the total corneal astigmatism, not only the anterior surface astigmatism). To achieve (long-term) correction of astigmatism, the IOL need to keep their postoperative rotational position. This was the weak point of the early toric implants; rotations as large as 30° were observed with the first plate haptic models. Today's implants however maintain their rotational position in an adequate way to achieve refractive stability.

Theoretically toric IOL implantation is indicated for cataract patients with corneal astigmatism of 0.75D or more, as this is usually seen as the clinical significant value of astigmatism. Poll and colleagues compared visual results regarding astigmatism correction in two patient cohorts (Poll et al. 2010). Of 192 eyes, 77 were provided with toric IOL, 115 were treated with limbal relaxing incisions (LRI). Preoperatively, groups differed only in manifest cylinder refraction, which was slightly higher in the toric IOL group. Postoperatively, the difference in manifest cylinder refraction was no longer observed (0.42D in the IOL group and 0.46D in the LRI group). Eyes with a preoperative astigmatism of ≥2.26D, however, more often reached a postoperative astigmatism of ≥20/40. Below this threshold, both procedures were comparable. Thus, it can be concluded that for reasons of better correction of high cylinders and at the same time no risk of regression of correction (due to,

**Fig. 7.1** Refractive, multifocal IOL (M-flex, Rayner). The rings represent areas of different refractive powers, for near and distance correction

**Fig. 7.2** Toric, aspheric, diffractive-refractive, circular, blue-light-filtering multifocal IOL (ReSTOR Toric, Alcon). The diffractive central zone allows for good near and distance visual acuity with small pupils; the peripheral zone is optimized for distance visual acuity with large pupils, for example, in night driving. The *three dots* indicate the cylinder axis

e.g., wound healing after performing LRI), toric IOL should be the procedure of choice to correct astigmatism when performing cataract surgery.

#### 7.4.2.3 Multifocal IOL

Implantation of multifocal IOL is today's gold standard procedure to achieve spectacle independency after cataract extraction for distance and near tasks simultaneously. Four major optical principles are used today: (a) refractive circular (Fig. 7.1) IOL, (b) diffractive circular IOL, (c) combinations of (a) and (b) (Fig. 7.2), and finally (d) refractive segmental IOL (Fig. 7.3). All these lenses use bifocal optics, generating two or more foci simultaneously. Depending on the distance of the fixated object, usually near at 30–40 cm and/or intermediate at 60–89 cm as well as far at ≥4 m, one of the foci and thus a clear image is located on the retinal plane. By neuronal suppression of the respective other picture, the patient can see clearly in the respective distance.

Kohnen et al. implanted aspheric multifocal IOL of the diffractive-refractive persuasion bilaterally in 93 cataract patients (Kohnen et al. 2009c). All patients significantly gained visual acuity for all evaluated distances. Six months

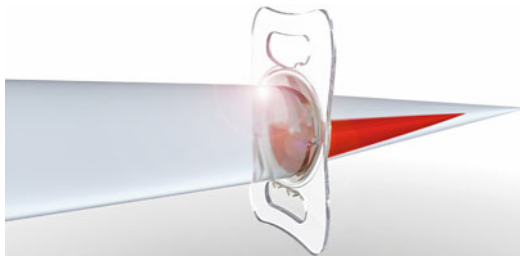

**Fig. 7.3** Refractive segmental multifocal intraocular lens (Mplus, Oculentis) with the major distance-focus segment as well as the smaller near-focus segment (*red*). The central IOL optic is used for distance focus as well

postoperatively, the mean uncorrected visual acuities were 0.03 ± 0.13 logMAR at 4 m, 0.20 ± 0.14 logMAR at 70 cm, 0.13 ± 0.15 logMAR at 60 cm, 0.05 ± 0.18 logMAR at 50 cm, and 0.04 ± 0.11 logMAR at 40 cm. Patients' preferred reading distance was 41 ± 4 cm. This value corresponds perfectly with the IOLs addition of 3D (which equals approx. 2.5D in glasses) and is thus reflected by the defocus curve, which peaks 40–50 cm with a visual acuity of −0.01 ± 0.11 logMAR. On a subjective satisfaction score from 1 (not satisfied) to 10 (extremely satisfied), patients' average rating was 8.3 ± 1.6. Eighty-eight percent of patients explained they where independent of spectacles after surgery. Several other trials evaluating different types of implants confirm these results in terms of visual acuity, patient satisfaction, and spectacle independency; these are among others Akaishi et al. (2010), Gunvant et al. (2011), and Patel et al. (2008).

Despite the excellent refractive results, all multifocal lenses suffer from inherent problems, caused by this principle of two or more simultaneous imaged foci. As both images, the clear one and the blurred one, appear on the retina, neuronal adaptation is required to suppress the blurred image. Furthermore, the light intensity is lower for each image in comparison to a monofocal lens, which transmits almost 100 % of the light (reflection and absorption being ignored) to one focus on the retina. Both effects lead to loses in contrast sensitivity and increased glare disability.

In most commonly used multifocal IOL this effect is not of clinical relevance anymore, if patient selection has been performed properly.

Hayashi and colleagues performed a controlled prospective trial, comparing two groups of patients. Each comprised 64 eyes of 32 patients. One group was implanted bilaterally with a monofocal aspheric IOL, the other with an aspheric diffractive-refractive +3D addition IOL of the same general IOL body design. The mean monocular and binocular uncorrected and distance-corrected visual acuity at 0.5 m and at 0.3 m were significantly better in the multifocal group than in the monofocal group (e.g., monocular distance-corrected visual acuity at 0.3 m: 20/33 in multifocal group vs. 20/94 in monofocal group). Distance and intermediate visual acuity at 0.7 and 1.0 m were similar between the two groups. No significant (but tendentious) differences were observed between groups in contrast acuity and glare acuity under photopic and mesopic conditions (Hayashi et al. 2009a). In another similar designed trial, Hayashi and coworkers evaluated a monofocal and a multifocal refractive IOL, both again with the same general IOL body, in 44 patients (22 in each group) up to 3 months after surgery. Mean VA in both the multifocal and monofocal IOL groups decreased gradually from far to near distances. When comparing the two groups, however, both uncorrected and best distance-corrected intermediate VA at 0.5 m and near VA at 0.3 m in the multifocal IOL group were significantly better than those in the monofocal IOL group, although there was no significant difference in far VA or in intermediate VA at 0.7 and 1.0 m. Photopic and mesopic contrast VA and glare VA were similar between the two groups (Hayashi et al. 2009b). Alio et al. looked at the third kind of multifocal IOL: the relatively new segmental refractive ones. Thirty-nine eyes were implanted with this lens and 35 with a refractive-diffractive IOL. Both groups were followed for 3 months. Uncorrected near visual acuity and distance-corrected near visual acuity were slightly better in the diffractive group than in the zonal refractive group, whereas intermediate visual acuity was slightly better in the segmental refractive group. Photopic contrast

sensitivity was significantly better in the zonal refractive group. Wavefront aberrations (total, higher order, tilt, primary coma) were significantly higher in the zonal refractive group than in the diffractive group (Alio et al. 2012).

It may be concluded from this trials that visual quality metrics are only tendentious but not significantly worse with the currently used multifocal IOL compared to the monofocal models. Different types of multifocal optic designs lead to comparable visual results. Furthermore, the patients benefit from increased near visual acuity in all tested multifocal IOL.

The patients presented, however, were trial patients and as such selected with much care. If the findings from controlled prospective randomized trials are applicable in daily practice depends on one major parameter: Is patient selection performed with due diligence? All methods for correction of presbyopia, from reading glasses to multiaddition glasses or contact lenses and multifocal implants, are compromise solutions only. They are not (yet?) able to restore the juvenile lenses' ability to accommodate. Thus, patients have to be screened for their multifocal lens eligibility not only in terms of anatomical properties but also for their individual visual requirements and their understanding of the IOL's optical principle as well as its advantages and disadvantages. Usually the in- and exclusion criteria should include:

- Potentially good binocular visual acuity after cataract extraction (no significant retinal pathologies and clear intraocular media and no irregular astigmatism and/or amblyopia).
- Corneal astigmatism within the range of the IOLs toricity.
- Patients with conditions associated with increased risk of zonular rupture should be excluded from surgery.
- Patients with zonular damage/rupture or capsular tear/rupture during the cataract extraction procedure that may lead to lens instability should not be implanted with multifocal IOL (backup lenses in the OR).
- Exclusion of patients with inability to fuse or focus for prolonged periods (e.g., due to strabismus, nystagmus).

Furthermore, patients should:

- Be able to understand the optical principle of the IOL and the resulting advantages and disadvantages according to their individual visual requirements in working life and leisure time. Patients are not always able to provide sufficient transfer; in this case, it is the surgeon's task to exclude patients whose individual visual requirements in daily life do not match the abilities of multifocal lenses.
- Be able to understand the advantages and disadvantages of multifocal IOL in comparison to monofocal IOL and the respective additional presbyopia corrections as well as compared to monovision.
- Receive thorough informed consent that there is a slight probability that they will nevertheless maybe need correction of a potential refractive error, either by contact lenses or refractive corneal surgery.

#### 7.4.2.4 Accommodating IOL

Accommodative IOL are meant to translate the movement of the ciliary muscle during accommodation into a dynamic change of the eye's refractive power (Klaproth et al. 2011). Three major types of accommodative IOL are being evaluated in the literature today: single-optic IOL, dual-optic IOL, and gel-optic IOL. The single-optic IOL's postulated effective principle is based on an anterior shift of the IOL caused by ciliary muscle contraction and thus increased pressure of the vitreous on the lens and the change in the IOL curvature. A movement of the IOL by 1 mm would theoretically result in a refractive power change of about 1.25D (Langenbucher et al. 2004). Until now, no clinical trial using physiological (non pharmaceutical) stimuli for accommodation has shown this movement; the principle of single-optic accommodating IOL has yet failed to prove its efficacy. Another approach is implant systems of two lenses, which are supposed to move in the respective opposite anterior or posterior direction. Here again, the ciliary muscle contraction is used to achieve this movement. Theoretically the accommodative amplitude of such lenses is higher than the amplitude of single-optic IOL. 2.5- to 4D might be achievable.

But again, the physiological stimulated proof of principle in the peer-reviewed literature is yet missing (Klaproth et al. 2011). However, some presentations and reports on trials using ultrasound biomicroscopy or dynamic aberrometry seem to show a movement of the IOL.

The third type of accommodating IOL, the gel-optic ones, also could not prove any movement or accommodation under physiological stimulation (Klaproth et al. 2011).

Generally it has to be noted that only such tests are suitable for proving accommodation that show a movement of the IOL, a change in the IOLs curvature, or at least dynamic changes in aberrometry for fixed pupil sizes. Visual acuity testing in different distances, defocus curves, or even reading charts is not acceptable.

Findl and Leydoldt conclude in their meta-analysis (Findl and Leydolt 2007) that the existing results from studies are not sufficient to prove dynamic changes of eyes implanted with the analyzed accommodating IOL when physiological stimulation is used. To the authors' opinion, this state has not changed, even with the introduction of some new IOL types (Klaproth et al. 2011). Some trials however show also positive effects for the patients, especially when evaluating intermediate vision. Factors like patient motivation (Leydolt et al. 2009), certain ocular aberrations like astigmatism (Nagpal et al. 2000; Nanavaty et al. 2006), or hidden multifocal lens designs (e.g., central steepening of the optics) seem to be responsible for these effects.

## 7.4.3 Basics of IOL Calculation

### 7.4.3.1 IOL Calculation

The fundamental requirement to achieve precise postoperative outcomes after cataract surgery is precise IOL calculation and therefore precise preoperative biometry. With the introduction and ongoing development of optical biometry, the precision of refractive cataract surgery results could be increased a lot, compared to the results achieved with the previously prevailing ultrasound measurements. Also IOL calculation formulas are much more advanced today. Early calculations were based for a good part on empirical data. Especially on long or short eyes, the deviation from target refraction was often very large. These formulas (e.g., SRK 1 and 2) are now considered obsolete. Today's IOL formulas suffer much less from these disadvantages as they are no longer based on empirical but measured data and mathematical-optical calculations. Formulas like Holladay 2 and Haigis offer predictable refractive results for all kind of eyes, even very long or short ones, if precise biometry is performed and the surgeon's personal "surgical factor" is evaluated in individual nomograms properly. However, even in ideal cases, there are some problems like the predictability of postoperative effective lens position (ELP), which leads to outliers in refractive predictability. Also an A-constant with a little "failure" can lead to postoperative myopia of one or more diopters. One group of eyes is even worse covered by standard IOL formulas: postcorneal refractive surgery eyes. These eyes will be one of the challenges for cataract surgeons in the twenty-first century, as more and more ametropic patients are treated with corneal refractive excimer and/or femtosecond laser procedures. The first of these patients now reach the cataract age, but more are to come and yet not all IOL calculation problems are solved for those patients.

### 7.4.3.2 IOL Calculation After Corneal Refractive Surgery

Accurate intraocular lens power calculation in eyes following laser corneal refractive surgery is known to be difficult. Often surgery in these patients resulted in unexpected hyperopic residual refractive error (Koch et al. 1989). There are mainly three reasons for these errors.

Classic keratometers only measure a central portion of the cornea (usually about 3 mm) and assume a prolate corneal anterior surface shape, as with normal corneas, whose curvature decreases from center to periphery. By treating these corneas with, for example, excimer surgery, this natural ratio of prolateness is lost. In myopic treatments the center is flattened and in hyperopic treatment is steepened. And it is this central area, keratometers measure, which results in false

refractive power estimations. However, this error is no longer of relevance for today's postkeratorefractive patients, as optical zones today are much bigger than in the beginning of corneal refractive excimer surgery.

Keratometers calculate the total corneal power by measurement of the corneal first surface and implement the influence of its thickness and posterior surface only by empirically changing the refractive index used for calculation. The natural ratio of anterior and posterior corneal curvature, however, is substantially changed by corneal refractive procedures. Thus, the refractive index used by keratometers (also keratometer index) leads to false, usually too large, corneal refractive power values. If such false values are used for IOL calculation, the refractive result of cataract surgery will be false, mostly hyperopic, resulting in patient dissatisfaction.

Another problem is the estimation of the effective lens position. Formulas such as Hoffer Q or Holladay II use the axial lengths and the anterior surface curvature to estimate ELP. As the ratio of corneal curvature to ELP is no longer normal in postcorneal refractive surgery eyes, the IOL positioning should not be based on it. The haggis formula e.g. is not affected by this error, as it does not use the corneal curvature for ELP estimation.

#### How to Avoid These Problems?

To avoid these factors and to improve the accuracy of IOL power calculations, several methods have been proposed: methods that use prerefractive surgery corneal curvature data, methods that are independent of preoperative data, and finally methods that combine both types of data.

The variety of methods and approaches itself is a problem again. Depending on available data and the surgical method used, different methods qualify for different patients. Most of the patients will not have the preoperative data available, and if they do, the quality of these measures cannot be estimated. A convenient option to select the appropriate formula is offered by the ASCRS. On the society's Web page, the ASCRS IOL calculator for postcorneal refractive surgery eyes can be found (http://iolcalc.org/). The user is asked to enter all available data for the respective patient here. The software evaluates from the given parameters (refraction, keratometry, topography, optical/ultrasound biometric data, target refraction, vertex, etc.) the available approaches for IOL calculation and provides the respective results for each formula as well as a mean IOL power value. The user can now choose the IOL of choice.

Haigis L formula (Haigis 2008) is another option of choice for the surgeon. As it is independent of historical data and implemented in, for example, the IOL Master software, postrefractive IOL calculation can be performed with no additional effort compared to all other standard IOL.

### 7.4.4 Surgical Techniques

One major goal of refractive cataract surgery in the twenty-first century, additionally to the removal of the blurred lens, has already been described: precise refractive outcome and optimized quality of vision according to the patients' visual requirements and preop ocular status. Furthermore, the avoidance of complications is still in focus of surgeons. And last but not least, the visual rehabilitation time is of interest, especially for the patient. This concept of fast and precise visual rehabilitation is often referred to as "instant vision." Instant vision is the clue for successful cataract surgery. It requires small or micro-incisional surgery, as only such incision can provide predictable refractive outcome that are too small to cause changes in corneal curvature and thus lower- and higher-order aberrations (surgical-induced astigmatism – SIA).

#### 7.4.4.1 Surgical-Induced Astigmatism

Incision sizes for implanting IOLs have a major influence on induced astigmatism, induced HOAs, wound stability, refractive stability and outcomes, postoperative rehabilitation time, and the risk for endophthalmitis. Incisions are smaller with injector systems than with IOL implantation using a forceps. For this reason and to attain less intraoperative contact with the conjunctival tissue and corneal endothelium, major companies provide injector systems for implantation of their

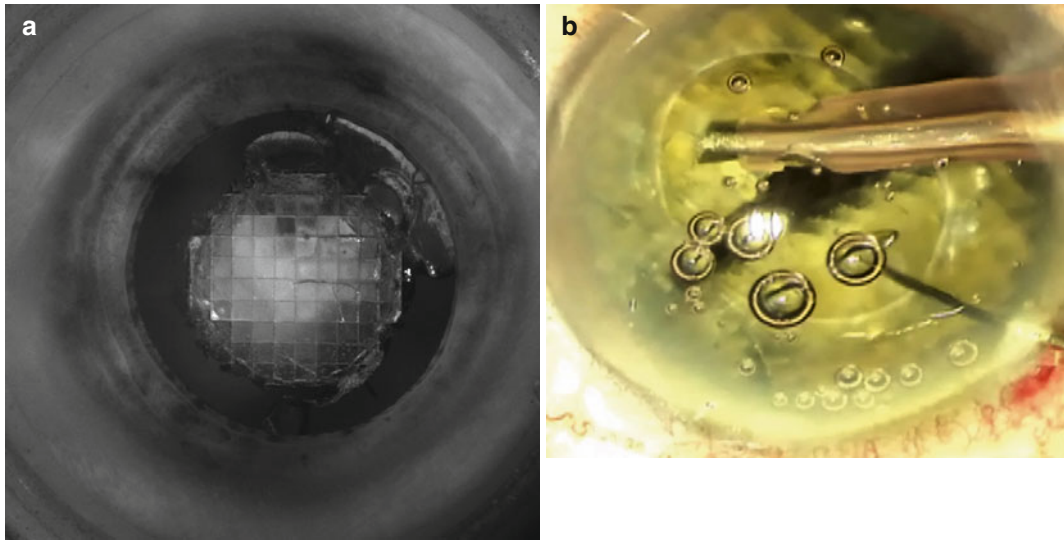


**Fig. 7.4** Laser phacoemulsification cutting sequence. (**a**) Femtosecond laser fragmentation of the lens followed by (**b**) removal of the lens fragments by a classical ultrasound device

IOLs. Several studies report that IOL implantation with injectors is safer than with a forceps. With progress in the development of IOL design and injector systems, decreasing incision sizes have been achieved. Thus, predictability of postoperative corneal astigmatism increases and the safe use of multifocal and/or toric IOL became much more predictable as well. Correction of astigmatism in cataract surgery can today be performed through micro-incisions with toric lenses, a method that also allows the surgeon to perform the same incision at the same location in a majority of patients. This again increases the predictability of the procedure. Factors like different magnitudes of induced astigmatism according to the location and size of the incision can be limited to a minimum.

### 7.4.4.2 Laser Phacoemulsification

In keratorefractive surgery photodisruptive femtosecond lasers are today a standard device to cut ocular tissue, namely, the cornea. The same laser systems are also used for different kinds of keratoplasty. A completely new field of application is lens surgery (cataract or refractive lens exchange) with femtosecond lasers. These laser systems are capable of fragmenting the natural lens, applying an anterior capsulotomy as well as a clear corneal incision and antiastigmatic corneal incisions (Fig. 7.4). Some systems additionally deliver the option to create LASIK flaps, keratoplasty, and other cuts. The currently worldwide launched systems have already been evaluated in different early trials. It becomes clear that they do provide superior cutting precision compared to standard procedures. On the other hand, the average treatment time appears to be longer, due to the increased requirements of preoperative preparations and intraoperative settings.

Nagy and colleagues published one of the first trials on the advantages of femtosecond lasers in cataract surgery in 2009. They did cut capsulotomies in porcine and a little series of human eyes. "For an intended 5-mm capsulorrhexis in porcine eyes, average achieved diameters were $5.88 \pm 0.73$ mm using a standard manual technique and $5.02 \pm 0.04$ mm using the femtosecond laser. Compared to control porcine eyes, femtosecond laser phacofragmentation resulted in a 43 % reduction in phacoemulsification power and a 51 % decrease in phacoemulsification time" (Nagy et al. 2009).

Kranitz et al. went one step further and did not only look at the precision of the capsulotomy, but also at the centration of 20 in-the-bag lenses after femtosecond laser capsulotomy and

manual capsulotomy with a follow-up of 1 year after surgery. They concluded that "More precise capsulotomy sizing and centering can be achieved with femtosecond laser. Properly sized, shaped, and centered femtosecond laser capsulotomies resulted in better overlap parameters that help maintain proper positioning of the IOL" (Kranitz et al. 2011).

However, if this significant benefit in precision and positioning has a clinical relevant influence on visual acuity has not been shown. Recently Filkorn and colleagues focused for the first time on this topic and evaluated the refractive predictability of intraocular lenses after femtosecond laser cataract surgery (Filkorn et al. 2012). They showed a better predictability of IOL calculations with femtosecond laser cataract surgery (77 eyes) compared to standard phacoemulsification (57 eyes) using SRK/T, Hoffer Q, and Holladay formulas. The mean predictive error 6 months after surgery was (0.58 ± 0.28) diopters in the femtosecond group and statistically worse (0.50 ± 0.38D) in the conventional group ($p = 0.04$). These differences became especially prominent in very long and very short eyes (Filkorn et al. 2012).

As with ultrasound phacoemulsification in its early years, there is a lot of discussion about the advantages and disadvantages with femtosecond laser cataract surgery as well. Do we really need this new tool? Yes, there is a benefit in precision, but the clinical benefit does not seem to be significant. However, most of the aforementioned trials are early trials with relatively small case numbers. It might be assumed, and it has already been published, that with an increasing number of surgeries, the surgery can get even more precise.

Bali and colleagues analyzed the development of outcomes and complications of femtosecond laser cataract surgery in their first 200 eyes. "There was a clear learning curve associated with the use of femtosecond lasers for cataract surgery. Adjustment to surgical technique and prior experience with a femtosecond laser seemed to flatten the learning curve" (Bali et al. 2012).

The future will tell us if femtosecond laser cataract surgery can replace today's gold standard, ultrasound. At the moment the ultrasound devices are still used after femtosecond laser lens fragmentation to remove the lens; however, not in every case ultrasound energy is applied. With developing techniques and increasing experience, this ratio might get even smaller. Especially patients implanted with premium IOL, like bi- or trifocal IOL, will benefit from this new precision, as they require minimal invasive surgery for most precise centration and positioning as well as predictable postoperative corneal astigmatism.

**Table 7.1** Complications of cataract surgery

| Complication | Frequency (Sun et al. 2010) |
|---|---|
| Cystoid macula edema | 1.5 |
| IOL dislocation | 1.1 |
| Retinal detachment | 0.7–1.23 |
| Bullous keratopathy | 0.3 |
| Endophthalmitis | 0.13–0.2 |

Modified from an analysis of the literature Powe et al. (1994); Erie et al. (2006a, b); Russell et al. (2006); ESCRS (2007)

## 7.4.5 Complications of Cataract Surgery

### 7.4.5.1 Intraoperative Complications

Complications of injective techniques for local anesthesia, such as retrobulbar hemorrhage, perforation of the globe, allergic reactions to the anesthetic agent, hypotension, and even respiratory paralysis due to accidental injection into the optic nerve and thus into the subarachnoid space, are extremely rare (0.066 %) now that anesthetics are increasingly being administered via eye drops and gels (Olsen and Olson 2000; Kohnen et al. 2004; Ezra and Allan 2007). The risk of intraocular hemorrhage is not markedly increased when topical anesthesia is used, even in patients taking anticoagulants (Patwardhan et al. 2006). Other potential intraoperative complications depend on the particular operative technique used (Lundstrom et al. 2007). These include, for example, damage resulting from the corneoscleral tunnel incision with bulbar hypotension, prolapse of uveal tissue through the wound (e.g., when alpha-1 antagonists are used), corneal injury due to separation of Descemet's membrane or corneal thermoinjury from the phacoemulsification tip, tearing of the capsular sac with subluxation of the IOL, and,

occasionally, incarceration or loss of the vitreous body or severe hemorrhage (choroidal effusion, expulsive hemorrhage) (Patwardhan et al. 2006).

#### 7.4.5.2 Postoperative Complications

Postoperative pain may be a sign of injury to the corneal epithelium, elevated intraocular pressure, or an intraocular infection (endophthalmitis). Endophthalmitis, one of the more serious postoperative complications of lens surgery (Table 7.1), is currently very rare (0.05 %) (Apple et al. 1992) when very strict antiseptic precautions are observed, yet markedly more common if older surgical techniques are used (0.36 %). It was shown very recently in a prospective, randomized multicenter study that an additional intracameral application of antibiotics significantly lowers the probability of endophthalmitis after cataract surgery (ESCRS 2007). If endophthalmitis does arise, it is very important for medical and/or surgical treatment to be provided as rapidly as possible. Other rare complications include wound dehiscence with bulbar hypotension, epithelial growth into the wound cleft, allergic scleral reactions to the eye drops, or subluxation of the IOL. Complications affecting the posterior segment of the eye include the occurrence of cystoid macular edema, which usually arises 1–3 months postoperatively and usually regresses in a further 6 months, though it produces holes in the retina on 0.4–5.4 % of cases. The latter may be associated with a so-called rhegmatogenic retinal detachment, that is, a detachment due to a tear in the retina (Lundstrom et al. 2007). The most common complication is postoperative posterior capsule opacification. While the frequency of postoperative posterior capsule opacification was as high as 50 % in 5 years in older publications (Erie et al. 2006a, b; Werner 2007), this has now been brought down to the much lower figure of less than 3 % in 3 years by improvements in surgical technique and the use of modern, sharp-edged flexible lenses (Zemaitiene et al. 2007). If a postoperative posterior capsule opacification should arise, it can usually be eliminated without difficulty by laser capsulotomy (opening the posterior capsule of the lens) with a neodymium-YAG laser. Nonetheless, preservation of a closed posterior capsule helps prevent postoperative complications such as retinal detachment and macular edema, which implies that a further reduction of the after-cataract rate would be desirable.

## 7.5 Future Procedures

### 7.5.1 Light Adjustable Lens

To solve the problem of postoperative residual refractive errors (either by miscalculation or normal variation), the principle of a light adjustable lens has been proposed. The body design of the implant looks similar to a classical silicone IOL. However, by irradiation with UV light, the special silicone molecules of the lens can be modified in orientation and structure. Therefore, the implant is able to achieve postoperative modification of its curvature and thickness and thus in its refractive power according to the residual refractive error. In practice, the residual refractive error is evaluated by subjective refraction. Afterwards, the UV light is applied, for one to three times in different sessions, until the final refractive status is achieved. Finally the lens is being irradiated with a higher UV intensity for fixation of its shape and thus refractive power. The possible applications are versatile: Corrections of residual hyperopia, myopia, and astigmatism have been performed already; the additional application of multifocal optics is also under investigation.

First trials prove the applicability of the system: surgery can be performed according to the known procedures; refractive results are good. Hengerer and colleagues followed 122 eyes implanted with the light adjustable lens over a postoperative period of 18 months. The mean postoperative spherical equivalent here was $0.03 \pm 0.17$ dpt (Hengerer et al. 2011). The low standard deviation is an indicator for the procedures' refractive precision.

A potential weakness of this lens is the intraocular load of UV light during refractive modification and fixation which might cause retinal damage. To minimize the retinal UV stress, the latest version of the light adjustable lens is equipped with special UB absorber material on the posterior surface. Hengerer and coworkers furthermore looked at potential UV-induced damages to the cornea and especially the corneal endothelium.

For this purpose 121 eyes were followed up for 12 months after the lenses final fixation of refractive power. The mean cumulative corneal irradiation dose was 61.47 ± 2.37 J/cm$^2$. The loss of corneal endothelial cells is given as 6.91 ± 2.37 % 2 weeks after fixation 6.57 ± 3.81 % 12 months after fixation. Corneal damage, other than the typically expected cataract surgery ones, was not observed (Hengerer et al. 2011).

### 7.5.2 Lens Refill

The idea to remove the lens from the capsular bag followed by a refilling of the latter with a material, similar to the natural lens, offers fantastic options. With only one surgery, a variety of problems could be solved: ametropia, presbyopia, and cataract. However, such a material has not been developed yet. Its main characteristics need to be a deformability similar to the natural lens, refractive indices similar to the natural lens, long-lasting biocompatibility and shape preservation, no leaking out of the capsular bag, and the ability to be injected through a microscopic capsulotomy. Even if those problems can be solved, others will arise: How can posterior capsule opacification be prevented (as we need the capsule intact and cannot provide any sharp edges)? Pharmacological approaches might help here. The second problem is the removal of the natural lens through the above mentioned micro-incision. Maybe the femtosecond laser phacoemulsification can offer a future option here. Different research groups focus on the lens refill. However, the concept is yet far away from a clinical application (Koopmans et al. 2003; Nishi et al. 2009).

**Conclusion**

Cataract surgery is becoming faster, more efficient, and more predictable. Not only can patients receive simple monoptics, but also highly sophisticated multifocal, refractive or diffractive, optics to assure best potential postoperative visual quality. The method which has been performed for many years, the phacoemulsification, is beginning to be replaced by the securer and preciser femtosecond laser. Further applications will show if this is a potential candidate to completely replace the "old- fashioned" surgery.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Akaishi L, Vaz R et al (2010) Visual performance of Tecnis ZM900 diffractive multifocal IOL after 2500 implants: a 3-year followup. J Ophthalmol 2010; pii: 717591. doi: 10.1155/2010/717591. Epub 2010

Alio JL, Plaza-Puche AB et al (2012) Comparison of the visual and intraocular optical performance of a refractive multifocal IOL with rotational asymmetry and an apodized diffractive multifocal IOL. J Refract Surg 28(2):100–105

Apple DJ, Solomon KD et al (1992) Posterior capsule opacification. Surv Ophthalmol 37(2):73–116

Bali SJ, Hodge C et al (2012) Early experience with the femtosecond laser for cataract surgery. Ophthalmology 119(5):891–899

Dupps WJ Jr, Kohnen T et al (2011) Standardized graphs and terms for refractive surgery results. J Cataract Refract Surg 37(1):1–3

Erie JC, Raecker MA et al (2006a) Risk of retinal detachment after cataract extraction, 1980–2004: a population-based study. Ophthalmology 113(11):2026–2032

Erie JC, Raecker ME et al (2006b) Risk of retinal detachment after cataract extraction, 1980–2004: a population-based study. Trans Am Ophthalmol Soc 104: 167–175

ESCRS (2007) Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. J Cataract Refract Surg 33(6):978–988

Ezra DG, Allan BD (2007) Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification. Cochrane Database Syst Rev (3):CD005276

Filkorn T, Kovacs I et al (2012) Comparison of IOL power calculation and refractive outcome after laser refractive cataract surgery with a femtosecond laser versus conventional phacoemulsification. J Refract Surg 28: 540–544

Findl O, Leydolt C (2007) Meta-analysis of accommodating intraocular lenses. J Cataract Refract Surg 33(3): 522–527

Gunvant P, Ablamowicz A et al (2011) Predicting the necessity of LASIK enhancement after cataract surgery in patients with multifocal IOL implantation. Clin Ophthalmol 5:1281–1285

Haefliger E, Neuhann T (1988) Neuhann capsulorhexis: a technic for reliable implantation of the capsule sack. Klin Monbl Augenheilkd 192(5):435–438

Haigis W (2008) Intraocular lens calculation after refractive surgery for myopia: Haigis-L formula. J Cataract Refract Surg 34(10):1658–1663

Hayashi K, Manabe S et al (2009a) Visual acuity from far to near and contrast sensitivity in eyes with a diffractive multifocal intraocular lens with a low addition power. J Cataract Refract Surg 35(12):2070–2076

Hayashi K, Yoshida M et al (2009b) All-distance visual acuity and contrast visual acuity in eyes with a refractive multifocal intraocular lens with minimal added power. Ophthalmology 116(3):401–408

Hengerer FH, Hutz WW et al (2011) Combined correction of axial hyperopia and astigmatism using the light adjustable intraocular lens. Ophthalmology 118(7): 1236–1241

Kelman CD (1967) Phaco-emulsification and aspiration. A new technique of cataract removal. A preliminary report. Am J Ophthalmol 64(1):23–35

Klaproth OK, Titke C et al (2011) Accommodative intraocular lenses – principles of clinical evaluation and current results. Klin Monbl Augenheilkd 228(8):666–675

Koch MJ, Kohnen T (1999) Refractive cataract surgery. Curr Opin Ophthalmol 10(1):10–15

Koch DD, Liu JF et al (1989) Refractive complications of cataract surgery after radial keratotomy. Am J Ophthalmol 108(6):676–682

Kohnen T (2009) New abbreviations for visual acuity values. J Cataract Refract Surg 35(7):1145

Kohnen T, Klaproth OK (2008) Aspheric intraocular lenses. Ophthalmologe 105(3):234–240

Kohnen T, Kasper T et al (2004) Ten-year follow-up of a ciliary sulcus-fixated silicone phakic posterior chamber intraocular lens. J Cataract Refract Surg 30(11): 2431–2434

Kohnen T, Baumeister M et al (2009a) Cataract surgery with implantation of an artificial lens. Dtsch Arztebl Int 106(43):695–702

Kohnen T, Klaproth OK et al (2009b) Effect of intraocular lens asphericity on quality of vision after cataract removal: an intraindividual comparison. Ophthalmology 116(9):1697–1706

Kohnen T, Nuijts R et al (2009c) Visual function after bilateral implantation of apodized diffractive aspheric multifocal intraocular lenses with a +3.0 D addition. J Cataract Refract Surg 35(12):2062–2069

Kollarits CR, Kollarits FJ et al (1982) The pupil dark response in normal volunteers. Curr Eye Res 2(4):255–259

Koopmans SA, Terwee T et al (2003) Polymer refilling of presbyopic human lenses in vitro restores the ability to undergo accommodative changes. Invest Ophthalmol Vis Sci 44(1):250–257

Kranitz K, Takacs A et al (2011) Femtosecond laser capsulotomy and manual continuous curvilinear capsulorrhexis parameters and their effects on intraocular lens centration. J Refract Surg 27(8):558–563

Langenbucher A, Reese S et al (2004) Pseudophakic accommodation with translation lenses–dual optic vs mono optic. Ophthalmic Physiol Opt 24(5):450–457

Leydolt C, Neumayer T et al (2009) Effect of patient motivation on near vision in pseudophakic patients. Am J Ophthalmol 147(3):398–405 e3

Lundstrom M, Wejde G et al (2007) Endophthalmitis after cataract surgery: a nationwide prospective study evaluating incidence in relation to incision type and location. Ophthalmology 114(5):866–870

Nagpal KM, Desai C et al (2000) Is pseudophakic astigmatism a desirable goal? Indian J Ophthalmol 48(3): 213–216

Nagy Z, Takacs A et al (2009) Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery. J Refract Surg 25(12):1053–1060

Nanavaty MA, Vasavada AR et al (2006) Analysis of patients with good uncorrected distance and near vision after monofocal intraocular lens implantation. J Cataract Refract Surg 32(7):1091–1097

Nishi Y, Mireskandari K et al (2009) Lens refilling to restore accommodation. J Cataract Refract Surg 35(2): 374–382

Olsen G, Olson RJ (2000) Update on a long-term, prospective study of capsulotomy and retinal detachment rates after cataract surgery. J Cataract Refract Surg 26(7):1017–1021

Patel S, Alio JL et al (2008) Comparison of Acri. Smart multifocal IOL, crystalens AT-45 accommodative IOL, and Technovision presbyLASIK for correcting presbyopia. J Refract Surg 24(3):294–299

Patwardhan A, Rao GP et al (2006) Incidence and outcomes evaluation of endophthalmitis management after phacoemulsification and 3-piece silicone intraocular lens implantation over 6 years in a single eye unit. J Cataract Refract Surg 32(6):1018–1021

Poll Jt, Wang L et al (2010) Correction of astigmatism during cataract surgery: toric intraocular lens compared to peripheral corneal relaxing incisions. J Refract Surg 27:165–171.

Powe NR, Schein OD et al (1994) Synthesis of the literature on visual acuity and complications following cataract extraction with intraocular lens implantation. Cataract Patient Outcome Research Team. Arch Ophthalmol 112(2):239–252

Ridley H (1952) Intra-ocular acrylic lenses after cataract extraction. Lancet 1(6699):118–121

Russell M, Gaskin B et al (2006) Pseudophakic retinal detachment after phacoemulsification cataract surgery: ten-year retrospective review. J Cataract Refract Surg 32(3):442–445

Sun X, Li P et al (2010) Investigating the effects of dimethylsulfoxide on hemodynamics during cortical spreading depression by combining laser speckle imaging with optical intrinsic signal imaging. Lasers Surg Med 42(9):649–655

Wang L, Dai E et al (2003) Optical aberrations of the human anterior cornea. J Cataract Refract Surg 29(8): 1514–1521

Wang L, Santaella RM et al (2005) Higher-order aberrations from the internal optics of the eye. J Cataract Refract Surg 31(8):1512–1519

Werner L (2007) Causes of intraocular lens opacification or discoloration. J Cataract Refract Surg 33(4):713–726

WHO (2011) http://www.who.int/en/ Accessed on January 1, 2012.

Zemaitiene R, Jasinskas V et al (2007) Influence of three-piece and single-piece designs of two sharp-edge optic hydrophobic acrylic intraocular lenses on the prevention of posterior capsule opacification: a prospective, randomised, long-term clinical trial. Br J Ophthalmol 91(5):644–648

# Neovascular Age-Related Macular Degeneration: Rationale for Current Treatment Guidelines

8

Connie J. Chen and Neil M. Bressler

## 8.1 Introduction

The antiangiogenic treatments for age-related macular degeneration have continued to evolve since the first FDA-approved anti-vascular endothelial growth factor (VEGF) therapy pegaptanib (Macugen, Eyetech Pharmaceuticals, Long Island, NY) was approved for use in neovascular age-related macular degeneration (AMD) in 2004 (U.S. Food and Drug Administration 2004; Gragoudas et al. 2004). While this treatment benefit appeared similar to photodynamic therapy (PDT) with verteporfin (Visudyne, QLT, Inc., Vancouver, Canada) (TAP Study Group 1999), subsequent studies with another anti-VEGF agent, ranibizumab (Lucentis, Genentech, South San Francisco, CA), appeared to be far superior to these earlier regimens. Specifically, the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominately Classic CHORoidal Neovascularization in AMD) and MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD) trials established efficacy for every 4-week ranibizumab for at least 2 years in neovascular AMD (Brown et al. 2006; Rosenfeld et al. 2006). Additional studies explored less-frequent dosing of ranibizumab (Holz et al. 2011; Lalwani et al. 2009; Regillo et al. 2008; Schmidt-Erfurth et al. 2011) and use of compounded bevacizumab for neovascular AMD (Avery et al. 2006; Bashshur et al. 2006; Rich et al. 2006; Spaide et al. 2006). However, until 2011, no large randomized trials supported the use of these alternative treatment approaches. In 2011 and 2012, respectively, the CATT (Comparison of Age-Related Macular Degeneration Treatment Trial) in the United States (CATT Research Group et al. 2011) and the IVAN (Inhibit VEGF in Age-related choroidal Neovascularization) trial in the United Kingdom (The IVAN Study Investigators 2012) evaluated whether bevacizumab was non-inferior to ranibizumab, and whether treatment regimens less frequent than every 4 weeks were non-inferior to every 4-week regimens. At the same time, new anti-VEGF therapies were being developed and tested. Most recently, the FDA approval of a new anti-VEGF therapy, aflibercept (EYLEA; Regeneron, Tarrytown, NY), has added yet another alternative for antiangiogenic treatment in AMD (Brown et al. 2011a, b; Heier et al. 2012). This chapter reviews the recent data for antiangiogenic approaches for neovascular AMD while also providing a framework for how these results may influence treatment decisions.

C.J. Chen • N.M. Bressler (✉)
Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University
School of Medicine and Hospital, Baltimore, MD, USA
e-mail: nbressler@jhmi.edu

## 8.2 ANCHOR and MARINA Trials

Ranibizumab (Lucentis, Genentech, South San Francisco) is a recombinant humanized monoclonal Fab fragment that inhibits all active forms of

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_8, 

VEGF-A. It is a chimeric molecule that includes a nonbinding human sequence and a high-affinity epitope derived from mice, which binds the antigen VEGF (Ferrara et al. 2006). The dosage of 0.5 mg given as a 0.05-cc intravitreal injection was approved in June 2006 for use in the treatment of AMD (Rosenfeld et al. 2006).

In the ANCHOR trial, patients with predominantly classic lesions (≥50 % of the total area of the lesion was classic CNV) involving the fovea were assigned randomly to (1) intravitreal ranibizumab 0.3 or 0.5 mg and sham verteporfin (Visudyne; Novartis AG, Basel, Switzerland) therapy or (2) sham ranibizumab injections and PDT with verteporfin (Brown et al. 2006). Participants received ranibizumab or sham injections monthly for 2 years. The decision to treat with verteporfin therapy was determined by the investigator based on results of angiography every 12 weeks (Brown et al. 2006). Using the primary outcome of visual acuity decline of <15 letters as a measure of efficacy, 96.4 % of the 0.5-mg group and 64.3 % of the verteporfin group met the primary goal ($P<0.001$) at the 1-year visit; these results were sustained through the 2-year visit. Visual acuity improved by ≥15 letters in 40.3 % the 0.5-mg group, as compared with 5.6 % of the verteporfin group ($P<0.001$) at 12 months (Brown et al. 2006), and this improvement was maintained through 24 months (Brown et al. 2009). At 24 months, mean visual acuity improved by 10.7 letters in the 0.5-mg ranibizumab group but decreased by 9.8 letters in the verteporfin group ($P<0.001$).

In the MARINA trial (Rosenfeld et al. 2006), patients with subfoveal CNV with minimally classic or occult with no classic lesion components accompanied by recent disease progression were randomized to either sham injections or intravitreal injections of ranibizumab (0.3 or 0.5 mg) for 24 months. Recent disease progression was defined as the presence of subretinal hemorrhage associated with CNV, recent loss of visual acuity >1 Snellen line (or equivalent), or growth of the CNV lesion by ≥10 % within the past month determined by fluorescein angiogram. Using the primary outcome of visual acuity decline of <15 letters as the measure of efficacy, 94.6 % of those in the 0.5-mg ranibizumab group and 62.2 % of those in the sham injection group met the primary goal ($P<0.001$) after 12 months of treatment, and these results were sustained through 24 months. At 12 months, visual acuity improved by ≥15 letters in 33.8 % of the 0.5-mg ranibizumab group, as compared with 5 % of the sham injection group ($P<0.001$). At 24 months, participants in the 0.5-mg ranibizumab group gained a mean of 6.6 letters or visual acuity, compared with a mean loss of 14.9 letters in the sham injection group ($P<0.001$) (Rosenfeld et al. 2006).

Data from the ANCHOR and MARINA trials not only demonstrated improvement in visual acuity but also improvement in patient-reported vision-related quality of life as measured by the National Eye Institute Visual Function Questionaire-25 (NEI-VFQ-25). Visual function was assessed as it related to activities that require both near vision (such as sewing) or distance vision (such as watching television). Patients treated in the ranibizumab group were more likely to have ≥10-point increase by NEI-VFQ-25, a clinically relevant increase, when compared against the sham injection group in the MARINA trial ($P<0.001$) (Chang et al. 2007) and the PDT group in the ANCHOR trial ($P<0.001$) (Bressler et al. 2009). These improvements in patient-reported outcomes were seen regardless of whether the treated eye is the better- or worse-seeing eye at the initiation of treatment (Bressler et al. 2010).

## 8.3 Non-inferiority Trials

### 8.3.1 Rationale for the Non-inferiority Trials

Until recently, intravitreal bevacizumab was used to treat choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) without strong evidence to determine if it was non-inferior or equivalent to ranibizumab. While multiple case series evaluating bevacizumab clearly showed average improvements in visual acuity, i.e., outcomes confirming its superiority to no treatment or PDT with verteporfin or pegaptanib, there were no studies to determine confidently if it was equivalent to ranibizumab.

However, since ranibizumab can cost approximately 40 times more per injection than the approximately $50 cost of a syringe of bevacizumab prepared for intravitreal use (Steinbrook 2006), bevacizumab was quickly adopted for use by the ophthalmic community worldwide (El-Mollayess 2011). Furthermore, prior to the availability of results from CATT and IVAN trials, the strongest evidence from clinical trials had suggested that every 4-week anti-VEGF treatment of CNV in AMD resulted in better visual acuity than regimens employing less-frequent treatment (Abraham et al. 2010; Holz et al. 2011; Regillo et al. 2008; Schmidt-Erfurth et al. 2011; Singer 2009). Thus, the National Eye Institute in the United States and the National Institute for Health Research in the United Kingdom independently designed and funded randomized, multicenter, non-inferiority trials to answer two important questions: (1) Does bevacizumab provide non-inferior visual acuity outcomes when compared with ranibizumab and (2) does either bevacizumab or ranibizumab, when provided on an as-needed or discontinuous basis, result in visual acuity outcomes which are non-inferior to monthly dosing (CATT Research Group et al. 2011; The IVAN Study Investigators 2012)? At the same time, the VIEW 1 and VIEW 2 trials were being conducted to evaluate whether less-frequent treatment could be achieved with aflibercept, a novel therapy with high affinity to VEGF and therefore theoretically longer treatment duration than either bevacizumab or ranibizumab (Brown et al. 2011a, b).

### 8.3.2 Non-inferiority Design

The CATT and the IVAN trials were powered to determine if bevacizumab was non-inferior to ranibizumab with respect to mean visual acuity change from baseline to 1 year. The non-inferiority design evaluates if bevacizumab is no less effective than ranibizumab by some margin. When considering an outcome as the mean change in visual acuity from baseline to 1 year, a difference between treatment regimens, in which the lower bounds of an appropriate confidence interval around that difference was no greater than 5 letters in the CATT study (Data analysis, statistical issues, and data monitoring 2010) and 3.5 letters in the IVAN study, was considered non-inferior. The 5-letter limit was chosen in the CATT design since numerous previous trials in which treatment regimens were considered marginally superior to control regimens in neovascular AMD, such as PDT with verteporfin or pegaptanib therapy, were approximately 6 letters greater (when comparing the mean change from baseline) in the new treatment compared with the standard treatment. Thus, it was judged that differences in CATT where the lower bounds of the confidence interval crossed 5 letters might not be considered equivalent but rather inferior. In the IVAN trial, a non-inferiority limit of 3.5 letters was chosen, presumably (Chakravarthy 2012) to represent less than one line of difference for the lower limit of the confidence interval. Using the confidence-level approach for evaluating non-inferiority, the lower limit of the confidence interval should lie entirely to the right of the non-inferiority limit for the treatment to be determined non-inferior (Fig. 8.1). Alternatively if the lower limit of the confidence interval lies to the left of the inferiority limit but does not cross zero, then the new treatment is determined to be either inferior (below the lower limit to be considered equivalent) or equivalent, but not superior to the control treatment.[1] If the lower limit of the confidence interval lies to the left of the inferiority limit and crosses zero, then the comparison is determined to be inconclusive (either inferior, equivalent, or if it crosses the +5 letter difference in this example, possibly superior). In the VIEW1 and VIEW2 trials, the statistical objective was to demonstrate that the 95.1 % (VIEW 1) or 95 % (VIEW 2) CI of the difference between ranibizumab and aflibercept in the proportion of subjects maintaining vision (avoiding loss of ≥15 ETDRS letters) after 52 weeks compared to baseline lay entirely below 10 % (the non-inferiority margin for this dichotomous outcome).

[1]Retreatment given if fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on fluorescein angiography judged at every 4 week assessments

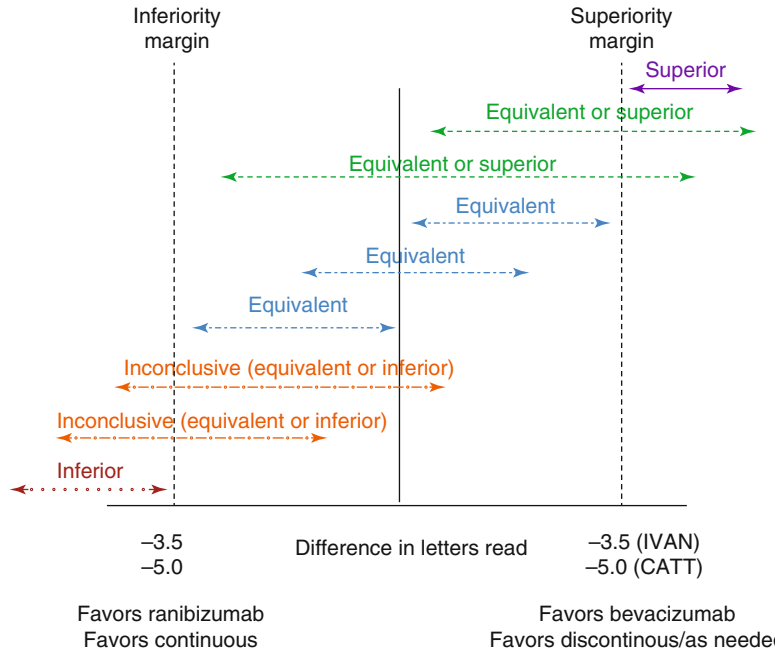


**Fig. 8.1** Example of potential outcomes of comparative effectiveness studies. Shown here are examples of possible outcomes of comparative effectiveness for visual acuity outcomes. Confidence intervals falling to the right of the inferiority margin are non-inferior. A non-inferior comparison is potentially equivalent or superior. An inconclusive comparison is potentially equivalent or inferior, therefore it fails non-inferiority

### 8.3.3 Primary Outcome of the CATT at 1 Year

The CATT is a 1-year multicenter, randomized, non-inferiority trial in which patients were assigned to four treatment arms: ranibizumab monthly, ranibizumab as needed, bevacizumab monthly, and bevacizumab as needed, with a second randomization at 1 year to evaluate secondary outcomes at 2 years. There were several major findings presented in the CATT 1-year report. Visual acuity gains when using bevacizumab every 4 weeks were equivalent (not inferior) to those using the gold standard of ranibizumab every 4 weeks. Furthermore, visual acuity gains when using ranibizumab as needed[2] were equivalent to those when ranibizumab was given every 4 weeks. However, visual acuity outcomes when comparing bevacizumab as needed based on every 4-week assessments with ranibizumab every 4 weeks were inconclusive, i.e., possibly equivalent but also possibly inferior or superior. The same was true when comparing bevacizumab as needed with bevacizumab every 4 weeks. CATT participants assigned to ranibizumab as needed received an average of approximately seven treatments in the first year and those assigned to bevacizumab as needed received an average of approximately eight treatments. Both medications resulted in substantial reduction in retinal thickness on OCT; however, ranibizumab achieved a greater mean decrease in foveal thickness than bevacizumab ($P=0.03$) at 1 year, and ranibizumab also had a greater proportion of patients with no fluid on OCT ($P<0.001$) at 1 year. Although no difference between ranibizumab and bevacizumab participants was identified with respect to proportions of participants who had myocardial infarction, cerebrovascular accidents, or endophthalmitis, the combined bevacizumab groups had a higher rate of systemic serious adverse events than the combined ranibizumab groups (24 % for bevacizumab, 19 % for ranibizumab). Somewhat paradoxically, the as-needed regimens with ranibizumab or bevacizumab also appeared to have a higher rate of systemic serious adverse events compared with every 4-week ranibizumab or bevacizumab, perhaps related to chance or perhaps related to better visual acuity in the every 4 week regimens leading to better health (CATT Research Group et al. 2011).

[2]Equivalency, on the other hand, using the boundaries defined by the CATT trial, requires that the two-sided confidence interval, which defines the range of plausible differences between two treatments, fall entirely within the interval −5 letter to +5 letters.

**Table 8.1** Retreatment criteria for as-needed treatment in non-inferiority trials

| Study | Year 1 | Year 2 |
|---|---|---|
| IVAN | Study participants were evaluated monthly (28–35 days) and were retreated if there was:<br>Increasing IRF on OCT or<br>Fresh blood or<br>Persistent IRF *and* a drop in visual acuity ≥10 letters over the past 3 months<br>If there was uncertainty, then FA was obtained and retreatment given if:<br>Fluorescein leakage >25 % of the lesion circumference or<br>Expansion of CNV | Study participants were evaluated monthly (28–35 days) and were retreated if there was:<br>Increasing IRF on OCT or<br>Fresh blood or<br>Persistent IRF *and* a drop in visual acuity ≥10 letters over the past 3 months<br>If there was uncertainty, then FA was obtained and retreatment given if:<br>Fluorescein leakage >25 % of the lesion circumference or<br>Expansion of CNV |
| CATT | Study participants were evaluated every 4 weeks with time-domain OCT and were retreated if there was:<br>Fluid on OCT (time domain)<br>New or persistent hemorrhage<br>Decreased visual acuity as compared with previous examination<br>Dye leakage or increased lesion size on FA[a] | Study participants were assigned with equal probability to one of four treatment groups defined by drug (ranibizumab or bevacizumab) and dosing regimen (every 4 weeks or as needed). Patients in the as-needed regimen were evaluated every 4 weeks and were retreated if there was:<br>Fluid on OCT (time domain or spectral domain) or<br>New or persistent hemorrhage or<br>Decreased visual acuity as compared with previous examination or<br>Dye leakage or increased lesion size on FA |
| VIEW1<br>VIEW 2 | All study participants were treated with a fixed regimen during the first 12 months | Study participants were reevaluated every 4 weeks and treated if:<br>Twelve weeks since previous injection or<br>New or persistent fluid on OCT or<br>Increase in central retinal thickness of ≥100 μm compared to lowest previous value or<br>A loss of ≥5 ETDRS letters from best previous score with recurrent fluid on OCT or<br>New onset of classic neovascularization or<br>New or persistent leak on FA or<br>New macular hemorrhage |

*FA* fluorescein angiography, *CNV* choroidal neovascularization, *IRF* intraretinal fluid, *OCT* optical coherence tomography
[a]Fluorescein angiography was performed at the discretion of the ophthalmologist

### 8.3.4 One-Year Results of the IVAN Trial

The IVAN trial, conducted in the United Kingdom, is a 2-year, multicenter, randomized, non-inferiority trial comparing bevacizumab and ranibizumab as well as continuous and discontinuous dosing with interim results provided at 1 year. Unlike the CATT, all patients were treated monthly (every 28–35 days) for the first three visits, and then patients randomized to the discontinuous group were retreated with a further cycle of 3 doses if they met prespecified OCT and clinical criteria. Specifically patients were retreated if there was any subretinal fluid on OCT, *increasing* intraretinal fluid on OCT, or fresh blood. If there was only persistent intraretinal fluid on OCT, then retreatment was given only if visual acuity had dropped ≥10 letters over the past 3 months. If there was uncertainty about these criteria, then a fluorescein angiogram was obtained and retreatment was given if there was fluorescein leakage >25 % of the lesion circumference or extension of choroidal neovascularization (Table 8.1). Based on this regimen, there were 7 injections given in the discontinuous versus 12 in the continuous group, resulting in 5 fewer injections. When compared with the

as-needed regimens in the CATT in which patients were treated with a mean of 7 injections at 1 year, the discontinuous dosing in the IVAN trial resulted in a similar number of treatments. The 1-year results in the IVAN trial revealed that the visual acuity outcomes when comparing bevacizumab with ranibizumab were inconclusive, specifically there was a difference of 1.99 letters in favor of ranibizumab and the 95 % confidence interval (−4.04 to 0.06) crossed the -3.5 letter non-inferiority limit (Fig. 8.2b). Although, vision outcomes when comparing discontinuous treatment with either bevacizumab or ranibizumab to continuous treatment with either bevacizumab or ranibizumab were equivalent (95 % CI −2.40 to 1.70; $P = 0.005$), it is unclear if discontinuous treatment with bevacizumab was equivalent, inferior, or inconclusive to discontinuous treatment with ranibizumab. The results of this latter situation seem important since ASRS Survey data suggest that most ophthalmologists in the USA give bevacizumab as a prn regimen rather than every 4 weeks, and the CATT data reported that comparison of vision outcomes using bevacizumab compared with ranibizumab every 4 weeks was inconclusive.

In IVAN, pooled analysis of OCT center point thickness at the fovea showed a difference of

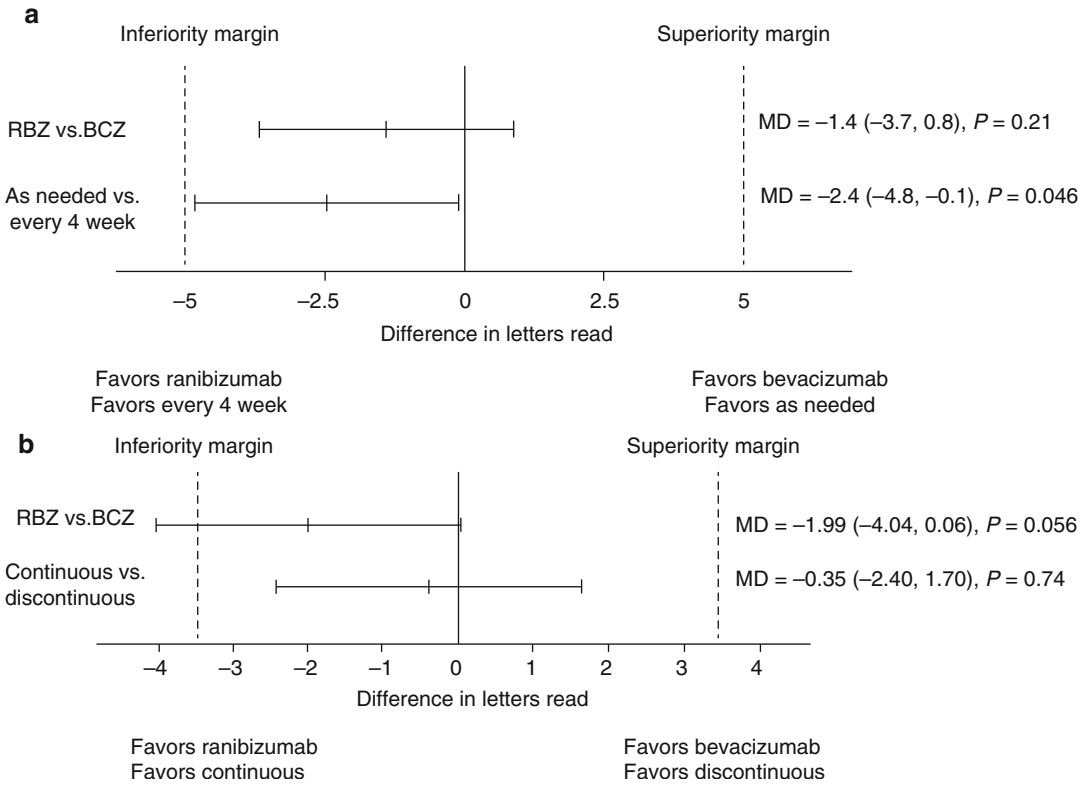


**Fig. 8.2** (**a**) CATT noninferiority comparison of primary endpoint: change in visual acuity at 2 years. Differences in mean change in visual acuity at 2 years and 95 % confidence intervals in patients treated with the same dosing regimen for 2 years (Adapted from CATT Research Group et al. (2012)). (**b**) IVAN noninferiority comparison of primary endpoint: change in visual acuity at 1 year. Differences in mean change in visual acuity at 1 year and 95 % confidence intervals in patients treated with the same dosing regimen. Negative values reflect a greater mean visual acuity at 1 year (Adapted from The IVAN Study Investigators (2012)). (**c**) VIEW 1 and VIEW 2 noninferiority comparison of primary endpoint: maintenance of vision at 52 weeks. Change in best-corrected visual acuity from baseline to week 52 in VIEW 1, VIEW 2, and integrated data. In each study and for all comparisons, the actual upper limit of the confidence interval of the difference between ranibizumab and VEGF Trap-Eye (≤3.1 %) was substantially below the pre-specified, clinically meaningful non-inferiority margin of 10% and also below 5 %. "2q8" = Aflib every 4 week for 3 doses than q8 week for one year (Adapted from Heier et al. (2012))

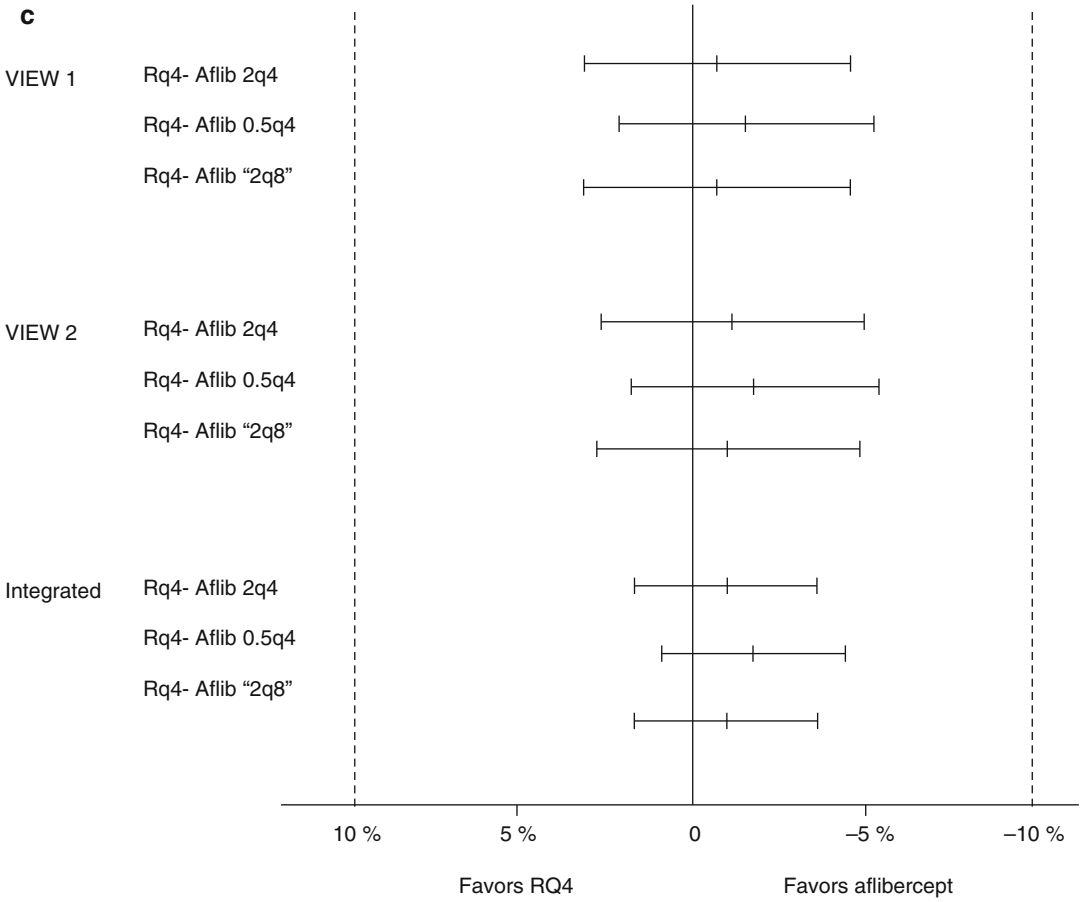


**Fig. 8.2** (continued)

22 μm favoring ranibizumab (95 % CI; 3.94–40.1) and a difference of 26.2 μm favoring continuous treatment (95 % CI, 8.14–44.2), consistent with the CATT. The safety data at 1 year in the IVAN trial differed from the 2-year CATT in that there were *fewer* arteriothrombotic events and reports of heart failure with bevacizumab (OR 0.23, 95 % CI 0.05–1.07; $P = 0.03$). In the IVAN study, a difference in the proportion of patients experiencing serious systemic adverse events, as in CATT, was more common with bevacizumab (12.5 %) than ranibizumab (9.6 %), and while this difference was not as great as that seen in CATT, it was in the same direction. A subsequent meta-analysis of all safety data by the IVAN investigators resulted in the posting of a patient safety letter available to the public (http://cteu.bris.ac.uk/trials/ivan/PatientSafetyLetter.pdf) (IVAN Patient Safety Letter 2012) stating that the analysis confirmed that people who were treated with bevacizumab had a slightly higher risk of having a serious systemic adverse event. Most of the adverse events that contributed to the excess risk affected the stomach and bowel.

More recently, additional risks in the community's use of bevacizumab were identified with respect to risks of serious ocular adverse events such as endophthalmitis, presumably due to poor adherence to sterile technique when compounding bevacizumab for intravitreal injection (Goldberg et al. 2012) or use of counterfeit bevacizumab (Wang et al. 2013). Other problems with compounding pharmacy techniques in general, rather than specific to bevacizumab preparation (Goodnough 2012; Martin et al. 2012), implicate the need for additional caution when considering the source where one might obtain bevacizumab for intravitreal injection.

**Table 8.2** Comparison between various treatment regimens

| Drug | Treatment interval | # Visits (2 year) | Mean # treatments[a] | Theoretical maximum treatments | Imaging required |
|---|---|---|---|---|---|
| Ranibizumab | Every 4 weeks | 26 | 22.4 | 26 | No |
| Bevacizumab | Every 4 weeks | 26 | 23.4 | 26 | No |
| Ranibizumab | Every 4-week exams with as-needed treatment | 26 | 12.6 | 26 | Yes |
| Aflibercept | Every 4 weeks × 3 doses, then every 8 weeks until 1 year, then every 4-week exams with as-needed treatment (minimum at least every 12 weeks) until 2 years | 21 | 12.2 | 21 | Yes |

[a]Mean number of treatments in CATT, VIEW 1, and VIEW 2 trials

### 8.3.5 One-Year Results of the VIEW 1 and VIEW 2 Trials

The phase 3 randomized, double-masked VIEW 1 and VIEW 2 trials provided safety and efficacy data for aflibercept in neovascular AMD with subfoveal involvement. These two trials were designed as non-inferiority studies in US and Canada (VIEW 1) and in Asia, Australia, and Europe (VIEW 2). Patients were included if they had subfoveal CNV (or juxtafoveal CNV with subfoveal subretinal fluid), best corrected visual acuity letter score of 73–25 (approximate Snellen equivalent 20/40–20/320) in the study eye, and CNV ≥ 50 % of the total lesion. They were excluded if there was prior ocular or systemic treatment for neovascular AMD or scar, fibrosis, or atrophy involving the fovea. Approximately 1,200 patients in each study were randomized to four fixed schedule treatment arms in the first year (ranibizumab 0.5 mg every 4 weeks, aflibercept 2 mg every 4 weeks, aflibercept 0.5 mg every 4 weeks, and aflibercept 2 mg every 4 weeks for 3 doses followed by q8 weeks). In the second year, study participants were treated on an as-needed schedule (Table 8.1). If no treatment was given for at least 12 weeks, then an injection was given so that all participants were treated at least every 12 weeks during the second year. The primary endpoint was the proportion of patients avoiding ≥15 letter loss at 1 year. Major secondary endpoints included mean change in visual acuity from baseline, percentage of patients who gained ≥15 letters, change in CNV area, change in central retinal thickness, and change in quality of life assessment by NEI-VFQ score at 1 year (Brown et al. 2011a, b).

One-year results showed that for the primary endpoint, all aflibercept arms were non-inferior to ranibizumab every 4 weeks. To demonstrate non-inferiority, the 95.1 % (VIEW 1) or 95 % (VIEW 2) CI of the difference between ranibizumab and aflibercept in the proportion of patients maintaining vision (avoiding loss of ≥15 ETDRS letters) after 52 weeks compared to baseline must lie entirely below 10 % non-inferiority margin (Fig. 8.2c). At the 52-week endpoint for VIEW1, the difference in proportion of patients maintaining vision between 0.5 mg aflibercept every 4 weeks and ranibizumab 0.5 mg every 4 weeks was a 1.5 % difference in favor of aflibercept (95 %CI; −2.1 to 5.1 %). The difference in proportion of patients maintaining vision between 2 mg aflibercept every 4 weeks and ranibizumab 0.5 mg every 4 weeks was a 0.7 % difference in favor of aflibercept (95 %CI; −3.1 to 4.4 %). The difference in proportion of patients maintaining vision between 2 mg aflibercept every 8 weeks and ranibizumab 0.5 mg every 4 weeks was a 0.7 % difference in favor of aflibercept (95 %CI; −3.1 to 4.5 %). Non-inferiority comparisons were similar for VIEW2 and are shown in Fig. 8.2c. Of note, while aflibercept every 4 weeks for 3 doses followed by every 8 weeks to 1 year was non-inferior to ranibizumab every 4 weeks, it is unknown if ranibizumab every 4 weeks for 3 doses followed by every 8 weeks also would be non-inferior to ranibizumab every 4 weeks.

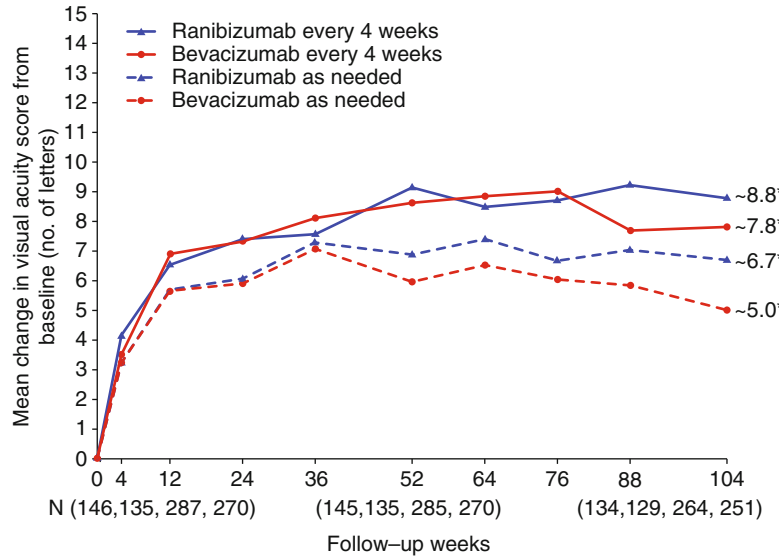


**Fig. 8.3** Mean change in visual acuity at 2 years in the CATT trial for patients treated with the same dosing regimen. The mean change in visual acuity from enrollment over time in patients treated with the same dosing regimen for 2 years. *Approximate point estimates based on visualization (Adapted from CATT Research Group et al. (2012))

## 8.4 Purpose of the 2-Year Results

Follow-up in CATT, VIEW 1, and VIEW 2 in year 2 were not designed to continue to determine if non-inferiority was maintained; IVAN was designed to determine if non-inferiority is maintained (likely to be published by the second half of 2013).

### 8.4.1 Two-Year Results for the CATT

In the second year of the CATT, patients in the every 4-week regimen were randomized to one of the following two regimens: (1) continued every 4-week treatment or (2) as-needed treatment, while continuing the same anti-VEGF assignment; patients initially assigned to as-needed treatment with either bevacizumab or ranibizumab had no change in their dosing regimen. With further randomization in the second year, there was an increase in the number of possible comparisons, loss of statistical power, and increased likelihood of an inconclusive result. Results were pooled by anti-VEGF regimen (bevacizumab as needed plus bevacizumab every 4 weeks, or ranibizumab as needed plus ranibizumab every 4 weeks) and treatment regimen (bevacizumab as needed plus ranibizumab as needed, or bevacizumab every 4 weeks and ranibizumab every 4 weeks). In the pooled data, the mean gain in visual acuity for bevacizumab versus ranibizumab was −1.4 letters (95 % CI: −3.7 to 0.8; $P=0.21$); the mean gain in visual acuity for ranibizumab and bevacizumab groups when given as needed with every 4-week assessment versus every 4-week treatment was −2.4 letters (95 % CI: −4.8 to −0.1; $P=0.046$) (Fig. 8.2b). Individual pairwise comparisons were not made between treatment arms, although the mean change from baseline was provided, and by year 2 (Fig. 8.3) the point estimate ranged from 8.8 for ranibizumab every 4 weeks to 5.0 for bevacizumab as needed, a difference of 3.8; calculating the 95 % confidence interval, the upper and lower bounds would be −7.3 to −0.3 for bevacizumab as needed, suggesting that this regimen likely is inferior to ranibizumab every 4 weeks. The mean change from baseline visual acuity for bevacizumab every 4 weeks was 7.8 letters, a difference of 1 letter worse compared with ranibizumab every 4 weeks; calculating the 95 % confidence interval, the upper and lower bounds would be −4.8 to 2.8 for bevacizumab every 4 weeks, suggesting that the comparison is inconclusive. The mean change from baseline visual acuity for ranibizumab as needed was 6.7 letters, a difference of 2 letters worse compared with ranibizumab

every 4 weeks; calculating the 95 % confidence interval, the upper and lower bounds would be −5.3 to 1.1 for bevacizumab monthly, suggesting that the comparison is inconclusive. In conclusion, the visual acuity outcomes in CATT suggest that bevacizumab or ranibizumab as needed with every 4-week assessment likely is inferior by a clinically relevant amount when compared to ranibizumab every 4 weeks, while bevacizumab every 4 weeks likely is equivalent to ranibizumab, and if it is slightly worse to ranibizumab every 4 weeks, the difference likely is not clinically relevant.

These results are supported by the anatomic outcomes in year 2. The ranibizumab group continued to have a greater proportion of patients without fluid on OCT at 2 years ($P<0.0003$), with the ranibizumab every 4-week group having the highest proportion of patients with a dry OCT (without intraretinal or subretinal fluid). While this same group was noted to have the highest proportion of geographic atrophy, it is unclear if that is because the absence of fluid in an area of geographic atrophy allowed one to grade that area as geographic atrophy while another eye with geographic atrophy and fluid only allowed one to grade that area as CNV. Alternatively, if the ranibizumab every 4 weeks actually *causes* geographic atrophy, there is little biologic rationale it is associated with a better visual acuity outcome for the group as a whole. It is possible that most of the geographic atrophy identified to date is within an area previously occupied by CNV and does not affect the visual acuity if overlying photoreceptors remain functional or if the atrophy is not in the center of the retina. In contrast, bevacizumab-treated participants demonstrated an increase in the area of CNV over 2 years when compared with ranibizumab-treated participants who demonstrated a mean decrease in the area of choroidal neovascularization ($P=0.006$).

Although there still was no difference detected in the rates of death, myocardial infarction, or stroke between the two anti-VEGF products, the bevacizumab group continued to demonstrate a higher rate of serious systemic adverse events in the second year, even when controlling for potential baseline differences which could have affected this outcome. The percentage of study participants with one or more serious systemic adverse event was 39 % in the bevacizumab group versus 31.7 % in the ranibizumab group (adjusted risk ratio 1.30, $P=0.009$). The 2-year safety results from IVAN likely will be available by the second half of 2013.

### 8.4.2 Two-Year Results for the VIEW 1 and VIEW 2 Trials

Unlike the first year, in the second year of the VIEW1 and VIEW 2 trials, study participants assigned to ranibizumab or aflibercept were treated with the same retreatment regimens, were evaluated every 4 weeks to determine need for retreatment (defined as new or persistent fluid on OCT, increase in central retinal thickness of ≥100 μm compared to lowest previous value, a loss of ≥5 ETDRS letters from best previous score with recurrent fluid on OCT, new onset of classic NV, new or persistent leak on FA, or new macular hemorrhage), and if no retreatment were applied for at least 12 weeks, then retreatment was mandatory. When comparing 2 mg every 8 weeks aflibercept and ranibizumab every 4 weeks in the integrated analysis, the visual acuity difference was 0.27 letters in favor of ranibizumab (95 % CI: −1.97 in favor of aflibercept to 2.49 in favor of ranibizumab), with all groups showing a slight decrease in mean visual acuity at the 2-year visit when compared with the 1-year visit. Between year 1 and year 2, an average of 4.2 injections were given in the group initially assigned to aflibercept in the 2 mg every 8 weeks, compared with 4.7 injections given in the group initially assigned to ranibizumab every 4 weeks (difference = 0.3 fewer injections with aflibercept, although the confidence interval around this point estimate was not provided). Since there was no comparison between year 1 and year 2 of the retreatment regimen chosen in VIEW 1 and VIEW 2 with ranibizumab every 4 weeks, it is unknown if the slight decline from year 1 to year 2 in VIEW 1 and VIEW 2 is due to the retreatment regimen allowing no treatment for as long as 12 weeks (Heier et al. 2011; Brown et al. 2011a, b).

### 8.4.3 Questions Pending for Year 2 of IVAN Trial

Since the mean difference in visual acuity between bevacizumab and ranibizumab was 1.99 letters in favor of ranibizumab, 95 % CI: 4.04 letters in favor of ranibizumab to 0.06 letters in favor of bevacizumab, the non-inferiority comparison by anti-VEGF product was inconclusive at 1 year. The 2-year results may help elucidate whether the comparison remains inconclusive, supports equivalency, or supports whether bevacizumab is inferior to ranibizumab. In addition, while not a planned analysis, based on the CATT results, it would be of interest to determine further safety data in the second year of the IVAN trial as it may also afford more insight into the systemic safety profiles of the two drugs.

## 8.5 Safety Considerations

### 8.5.1 Safety Data for Bevacizumab and Ranibizumab

The 2-year CATT showed that ocular adverse events were infrequent with 4 of 599 (0.7 %) ranibizumab patients and 7 of 586 (1.2 %) bevacizumab patients resulting in endophthalmitis ($P=0.38$) (Martin et al. 2012). Uveitis, retinal detachment, retinal tear, or vascular occlusion each occurred in less than 1 % of patients. Rates of ocular adverse events seen in the IVAN trial appeared similar (The IVAN Study Investigators 2012). As noted earlier, one should consider as well the reports of anti-VEGF product contamination during compounding of bevacizumab, leading to clusters of endophthalmitis cases in certain areas (Goldberg et al. 2012), and consider preparation which might minimize these occurrences (Wykoff et al. 2011a).

With respect to systemic adverse events, data from the first and second year of follow-up in the CATT reported one or more serious systemic adverse event (e.g., pneumonia, urinary tract infections, and gastrointestinal disorders) to be more likely with bevacizumab group compared with ranibizumab ($P=0.004$) (Martin et al. 2012). These results require further study as it remains unclear if these differences are due to an effect of one anti-VEGF agent versus another, or due to other confounding factors, such as better visual acuity in the fixed-dosing regimen patients leading to better visual acuity, with the better visual acuity accounting for the fewer serious systemic adverse events. Of note, the 1-year data from the IVAN trial with respect to serious systemic adverse events showed results in a similar direction between bevacizumab and ranibizumab (OR 1.35; 95 % CI: 0.8–2.27; $P=0.25$) (The IVAN Study Investigators 2012), as in the CATT.

While there currently are nine warnings and precautions regarding systemic adverse events believed to be causally related to bevacizumab reported from oncology studies (including gastrointestinal perforation, surgery and wound healing complications, hemorrhage, non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome, proteinuria, and infusion reactions (http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf)) (Bevacizumab project insert 2012), dosages given to oncology patients are much greater than those given to ophthalmology patients. While reports of intravitreal ranibizumab (Brown et al. 2006) have concentrated on arterial thromboembolic events because these events were numerically higher than those identified among control groups, especially among patients with a prior history of a cerebrovascular accident, the overall frequency of the events has been too small to rule out the possibility that the increased number was due to chance alone, even in pooled analyses (Bressler et al. 2012). These safety issues need continued assessment as results of other comparative trials become available.

### 8.5.2 Safety Data for Aflibercept

Integrated 1-year safety data for VIEW1 and VIEW2 could not identify a difference in safety when aflibercept is dosed either every 4 weeks or every 8 weeks following every 4-week dosing for 3 consecutive visits.

### 8.5.3 Endophthalmitis and Prophylaxis

Intravitreal injections are complicated by endophthalmitis in approximately 1 out of every 1,000–5,000 injections (McCannel 2011; Moshfeghi et al. 2011). Though suggested guidelines have been developed based on round table discussions (Aiello et al. 2004), there is substantial variability in endophthalmitis prophylaxis among retina specialists (Green-Simms et al. 2011). A recent retrospective study of over 27,000 intravitreal injections showed that a difference in the risk of endophthalmitis could not be detected when taking into account lid speculum use, conjunctival displacement, and hemisphere of injection, or intravitreal medication did not affect risk of developing endophthalmitis (Shah et al. 2011), though in a recent survey of retinal physicians, 92 % report that they routinely use a lid speculum (Green-Simms et al. 2011).

Povidone-iodine, an inexpensive antiseptic that has rapid kill time (15–120 s), has shown to be bactericidal at a range of concentrations 0.1–10 % (Berkelman et al. 1982). In large nonrandomized studies of prophylaxis before cataract surgery, there have been no reported cases of bacterial resistance (Speaker and Menikoff 1991). The most common adverse reactions are related to its irritant effect on the ocular surface or an allergic contact dermatitis (Wykoff et al. 2011b), and all clinical trials evaluating intravitreal injections for AMD recommend the use of povidone-iodine over the injection site just prior to the injection.

Several studies have examined preinjection and postinjection antibiotic prophylaxis and emerging antibiotic resistance trends. Preinjection topical fluoroquinolones, when used with povidone-iodine, have not been shown to confer any additional benefit compared with povidone-iodine alone (Moss et al. 2009). Retrospective reviews have suggested that the endophthalmitis rate is no different with the use of postinjection antibiotics (Bhatt et al. 2011). In fact recent studies have suggested that postinjection antibiotics may in fact lead to antibiotic resistance of the ocular and nasopharyngeal flora and selection of more multidrug-resistant strains (Dave et al. 2011), and prospective studies across numerous US sites by the Diabetic Retinopathy Clinical Research Network suggest that the endophthalmitis rate is no higher, and possibly lower, when preinjection and postinjection antibiotics are not used, provided the anti-VEGF agent is prepared in a sterile fashion before injection, a lid speculum is used, and povidone-iodine is placed over the injection site just prior to injection (Bhavsar et al. 2012).

## 8.6 Rationale for Two Proposed Treatment Algorithms for Choroidal Neovascularization from Age-Related Macular Degeneration

Figure 8.4. CNV Treatment Algorithm in AMD.

### 8.6.1 Fixed-Dosing Regimens

Synthesizing the data from MARINA, ANCHOR, PIER, CATT, VIEW 1, VIEW 2, and IVAN, one of two regimens (fixed dosing versus as needed) among three different anti-VEGF agents (aflibercept, bevacizumab, and ranibizumab) can be considered. Given the slight decline in mean visual acuity from year 1 to year 2 with either aflibercept or ranibizumab when dosing was not fixed at 4- or 8-weekly intervals, and given the likelihood that this decline might continue at 3, 4, and 5 years after treatment has been initiated, patients should be cautioned that retreatment regimens based on visual acuity or OCT or fluorescein angiography or other parameters which result in withholding treatment for greater than 8 weeks may increase their chances of permanent (PIER) visual acuity loss (Abraham et al. 2010) when using ranibizumab or aflibercept. Only aflibercept, and not ranibizumab or bevacizumab, was evaluated at a q8-week fixed-dosing regimen following three every 4-week injections to demonstrate equivalency to every 4-week ranibizumab; thus, one cannot conclude that similar equivalency would not have been obtained if ranibizumab or

* Active neovascularization is defined as leakage on FA and fluid within or below the retina or under the retinal pigement epithelium as seen on OCT (CATT Research Group 2011).

** Treatment with ranibizumab, bevacizumab, and aflibercept likely no difference *within* regimens (fixed or as needed). Patients not bound by financial constraints should consider safety information for bevacizumab (CATT Research Group 2011; IVAN Study Investigators 2011; Heier 2012).

*** In IVAN patients had study visits every month (28–35 days), and in CATT patients were had study visits 4 weeks (28 days). It remains unknown if less frequent visits would result in the same or inferior outcomes.

† If any lesion component is threatening the fovea consider treatment with anti-VEGF therapy versus close observation.

†† See Table 8.1 for retreatment criteria for IVAN and CATT trials.

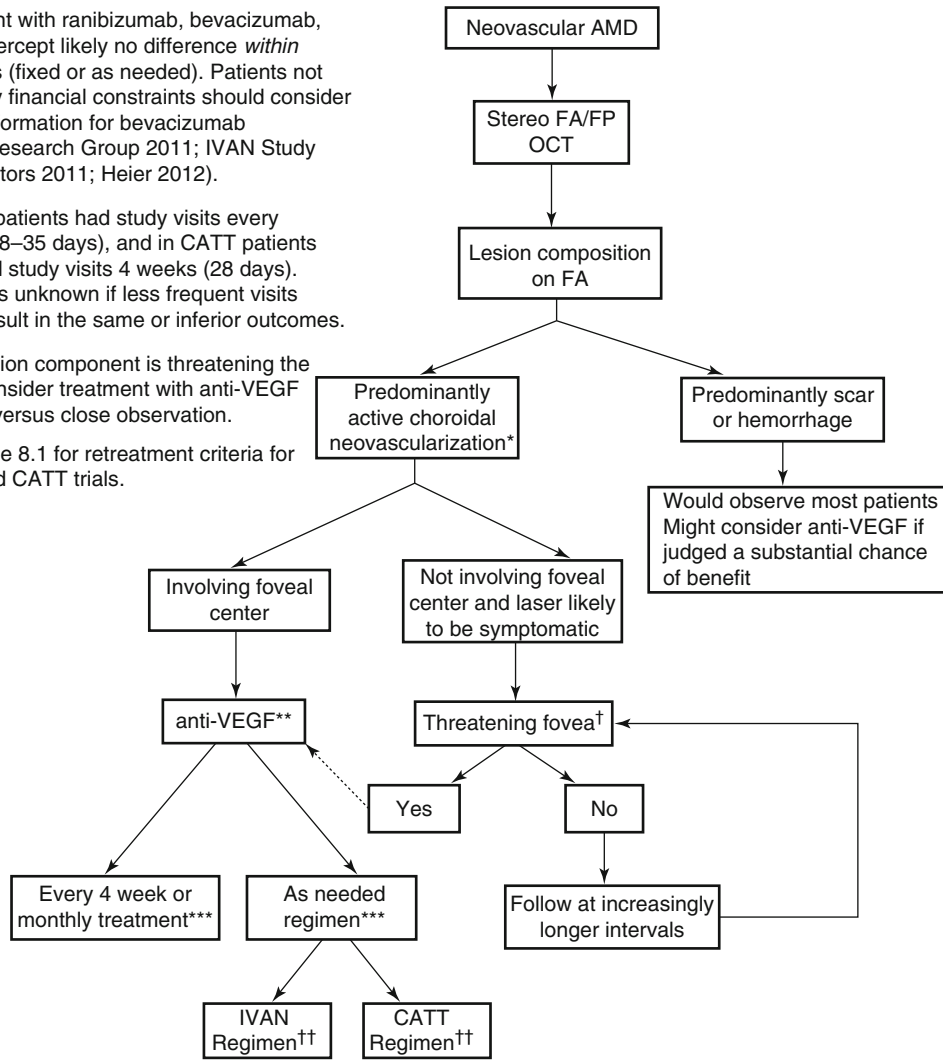


**Fig. 8.4** Proposed treatment algorithms for CNV from AMD. *AMD* age-related macular degeneration, *FA* fluorescein angiogram, *FP* fundus photographs, *OCT* optical coherence tomography, *anti-VEGF* anti-vascular endothelial growth factor. © Johns Hopkins University

bevacizumab were applied in this way. For now, one is left with considering a fixed regimen of ranibizumab every 4 weeks, or bevacizumab every 4 weeks, or aflibercept every 4 weeks for 3 doses followed by every 8 weeks to obtain mean improvements in visual acuity that do not show a decline for a group of patients treated in this way out to 1 year. One then must weigh the safety issues with bevacizumab versus ranibizumab or aflibercept, versus the markedly decreased cost of bevacizumab when given every 4 weeks compared with ranibizumab every 4 weeks or aflibercept in the first year given every 4 weeks for 3 doses followed by every 8 weeks.

Beyond 1 year, no data are available with respect to a fixed regimen of aflibercept at either

every 4 or every 8 weeks compared with every 4-week ranibizumab. There are data to suggest that both ranibizumab every 4 weeks and bevacizumab every 4 weeks in the second year of treatment result in sustained gains of vision for a group as were noted in the first year of treatment, and again, one must weigh the increased risk of serious systemic adverse events with bevacizumab versus the decreased costs if considering an every 4-week regimen.

### 8.6.2 As-Needed Regimens

Despite the data which do not support the use of as-needed regimens (CATT Research Group et al. 2011; Suñer and The HARBOR Study Group 2012) with bevacizumab, and suggestions that as-needed regimens with ranibizumab or aflibercept in year 2, while not inferior to a clinically relevant degree, may lead to a slight decline in visual acuity compared with continued every 4-week dosing of ranibizumab, this decline might become clinically relevant if it were to continue from year 2 to year 3 of treatment and thereafter.

The financial impact of fixed-dosing regimens as described above versus as-needed dosing is substantial. Furthermore, every 4- to 8-week regimen exposes patients to more injections over the remaining life of the patient (typically at least 10 years), placing patients at increased risk of both serious ocular complications (i.e., endophthalmitis) and potentially serious systemic adverse events. It should be noted that even in the as-needed regimens undertaken in the IVAN and CATT, every 4-week follow-up was performed when treatment was withheld to try to detect deterioration promptly which would warrant resumption of treatment from the start of the study, and in VIEW1 and VIEW2, every 4-week follow-up was performed after the 1-year time point, when a fixed regimen was discontinued (except to give aflibercept or ranibizumab at least every 12 weeks if not indicated based on specific parameters more frequently).

When considering which as-needed regimen should be used, it should be noted that all as-needed regimens recommended retreatment if the OCT showed any evidence of thickening or fluid accumulation, or new hemorrhage without such OCT abnormalities. Furthermore, even in the absence of such OCT abnormalities or new hemorrhage, studies have shown that fluorescein angiography might detect new fluorescein leakage (Khurana et al. 2010) to consider resuming or continuing treatment as well.

As with fixed regimen dosing, if one were choosing an as-needed regimen with every 4-week monitoring, and the patient or the patient's insurance precluded the ability to afford aflibercept or ranibizumab, but permitted bevacizumab therapy, then bevacizumab should be considered. However, the patient should be informed of the likelihood that the vision results for a group of patients receiving this regimen are not likely equivalent by year 2 compared with every 4-week ranibizumab, and the likelihood of remaining equivalent may continue to decline after year 2. If the patient or the patient's insurance did not preclude the ability to afford aflibercept or ranibizumab, then the safety findings which require further study from CATT and IVAN regarding bevacizumab, with additional safety findings to be provided by the year 2 results from IVAN, with the safety concerns of compounding, along with the costs to society, need to be reviewed with the patient in order to determine if bevacizumab rather than aflibercept or ranibizumab should be used in an as-needed regimen.

## 8.7 Future Considerations

### 8.7.1 Earlier Detection of CNV and Monitoring After Initiating Treatment for CNV

Large-scale studies have demonstrated that the final visual acuity outcome is better when visual acuity is better and when CNV lesions are smaller at the initiation of therapy (Boyer et al. 2007; Kaiser et al. 2007). However, patients often do not recognize conversion to neovascular AMD, especially when the fellow eye remains unaffected and visual acuity in the affected eye is relatively good. Improvements in home monitoring,

such as are being pursued with the preferential hyperacuity perimeter (Foresee PHP, Notal Vision, Tel Aviv, Israel) (Alster et al. 2005), may be valuable in this regard (Loewenstein et al. 2010). Home monitoring with this device or others also may have a role after initiating treatment for CNV when treatment in an as-needed regimen is withheld in order to detect worsening which might warrant resumption of treatment before the patient notices a change in vision (Querques et al. 2011).

### 8.7.2 New Strategies for Avoiding Indefinite Treatments at 4- to 8-Weekly Intervals

Many novel therapies are currently in development and may have promise in targeting the angiogenesis pathway or CNV formation to avoid fixed-dosing regimens at 4–8 weeks indefinitely while maintaining vision for years following initiation of treatment (Yuan and Kaiser 2011; Zarbin and Rosenfeld 2010). Targets of upregulation of VEGF, or identification of inhibitors of downstream VEGF targets, represent one approach (Nguyen et al. 2012; Nussenblatt et al. 2010). Other targets of angiogenesis include therapeutics that block the platelet-derived growth factor pathway, modulators of endothelial proliferation and migration, and the complement cascade (Kernt et al. 2012; Xie et al. 2009; Patel 2009; Ramakrishnan et al. 2006; Anderson et al. 2010; Weismann et al. 2011). In addition, alternative strategies for delivering anti-VEGF products, such as adeno-associated virus-encoded sequences (Pechan et al. 2009) or nanotechnology techniques, are being pursued, including the use of microspheres, nanospheres, or liposomes for sustained delivery (Kim et al. 2012; Hsu 2007).

**Conclusion**

With strong evidence from the CATT, VIEW 1 and VIEW 2 trials, and IVAN trial, clinicians now have two regimens (fixed versus as needed) among three anti-VEGF agents for treatment of neovascular AMD. While cost and burden of frequent visits influence the choice, the impact of these choices are more readily understood with the results of recent comparative effectiveness trials. Forthcoming 2-year IVAN trial data may reveal new findings, along with other comparative effectiveness trials across anti-VEGF agents that may impact the treatment guidelines discussed herein. For now, use of a fixed-dosing regimen no less frequently than every 8 weeks indefinitely appears to be more likely to sustain visual acuity outcomes that are attained following the initiation of treatment. While little clinically relevant differences across anti-VEGF agents have been identified when such fixed-dosing regimens are followed, an increase in serious systemic adverse events with bevacizumab requires further study and needs to be taken into account when finances might permit the use of aflibercept or ranibizumab in a fixed-dosing regimen. Furthermore, visual acuity outcome differences across agents when dosing regimens less frequent than every 4–8 weeks need to be clarified, although data suggest that bevacizumab as needed no longer may be equivalent to ranibizumab every 4 weeks by 2 years after treatment. Novel treatments that target different pathways in the angiogenesis cascade and alternative anti-VEGF delivery systems remain in development and could influence the considerations presented herein. Regardless, the availability of anti-VEGF products for neovascular AMD has had a profound impact on both the expected (Bressler et al. 2011) and actual (Campbell et al. 2012) number of cases of blindness from AMD as ophthalmologists await additional options for the treatment armamentarium of neovascular AMD.

**Acknowledgments**

**Disclosures**

From the Retina Division, Department of Ophthalmology, the Johns Hopkins University School of Medicine and Hospital, Baltimore, MD. Supported by Research to Prevent Blindness and the James P. Gills Professorship at The Johns Hopkins University. Supporters and The Johns Hopkins University had no role in the preparation, review, or approval of the manuscript.

Ethical standards: informed consent – not applicable; Animal rights – not applicable

**Financial Disclosures**

Dr. Neil Bressler is principal investigator of grants at The Johns Hopkins University sponsored by the following entities (not including the National Institutes of Health): Abbott Medical Optics Inc.; Alimera Sciences; Allergan USA, Inc.; Bausch & Lomb Incorporated; Bayer; Carl Zeiss Meditec, Inc.; DIAGNOS INC; ForSight Labs, LLC; Genentech, Inc.; Genzyme Corporation; Lumenis Inc.; Notal Vision; Novartis Pharma AG; Ora, Inc.; Pfizer Inc.; QLT Inc.; Regeneron Pharmaceuticals, Inc.; Research to Prevent Blindness; Steba Biotech S.A.; and The EMMES Corporation. Dr. Susan Bressler (spouse) is coinvestigator of grants at The Johns Hopkins University sponsored by the following entities (not including the National Institutes of Health): Bausch & Lomb Incorporated; Genentech, Inc.; Notal Vision; and Novartis Pharma AG. Grants to investigators at The Johns Hopkins University are negotiated and administered by the institution (such as the School of Medicine) which receives the grants, typically through the Office of Research Administration. Individual investigators who participate in the sponsored project(s) are not directly compensated by the sponsor but may receive salary or other support from the institution to support their effort on the project(s). Dr. Susan Bressler is a member of the CATT Data and Safety Monitoring Committee and has not reviewed or seen or discussed this editorial prior to publication.

Dr. Connie Chen has no financial disclosures.

## References


Abraham P, Yue H, Wilson L (2010) Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. Am J Ophthalmol 150:315–324.e1

Aiello LP, Brucker AJ, Chang S, Cunningham ET Jr, D'Amico DJ, Flynn HW Jr, Grillone LR, Hutcherson S, Liebmann JM, O'Brien TP, Scott IU, Spaide RF, Ta C, Trese MT (2004) Evolving guidelines for intravitreous injections. Retina 24:S3–S19

Alster Y, Bressler NM, Bressler SB, Brimacombe JA, Crompton RM, Duh YJ, Gabel VP, Heier JS, Ip MS, Loewenstein A, Packo KH, Stur M, Toaff T, Preferential Hyperacuity Perimetry Research Group (2005) Preferential Hyperacuity Perimeter (PreView PHP) for detecting choroidal neovascularization study. Ophthalmology 112:1758–1765

Anderson DH, Radeke MJ, Gallo NB, Chapin EA, Johnson PT, Curletti CR, Hancox LS, Hu J, Ebright JN, Malek G, Hauser MA, Rickman CB, Bok D, Hageman GS, Johnson LV (2010) The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. Prog Retin Eye Res 29:95–112

Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ (2006) Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 113:363–372.e5

Bashshur ZF, Bazarbachi A, Schakal A, Haddad ZA, El Haibi CP, Noureddin BN (2006) Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. Am J Ophthalmol 142:1–9

Berkelman RL, Holland BW, Anderson RL (1982) Increased bactericidal activity of dilute preparations of povidone-iodine solutions. J Clinl Microbiol 15: 635–639

Bevacizumab project insert. http://www.gene.com/gene/products/information/pdf/avastin -prescribing.pdf. Accessed 20 May 2012

Bhatt SS, Stepien KE, Joshi K (2011) Prophylactic antibiotic use after intravitreal injection: effect on endophthalmitis rate. Retina 31:2032–2036

Bhavsar AR, Stockdale CR, Ferris FL 3rd, Brucker AJ, Bressler NM, Glassman AR, Diabetic Retinopathy Clinical Research Network (2012) Update on risk of endophthalmitis after intravitreal drug injections and potential impact of elimination of topical antibiotics. Arch Ophthalmol 130:809–810

Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR, MARINA Study Group (2007) Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 114:246–252

Bressler NM, Chang TS, Fine JT, Dolan CM, Ward J, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) Research Group (2009) Improved vision-related function after ranibizumab vs photodynamic therapy: a randomized clinical trial. Arch Ophthalmol 127:13–21

Bressler NM, Chang TS, Suner IJ, Fine JT, Dolan CM, Ward J, Ianchulev T, MARINA and ANCHOR Research Groups (2010) Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. Ophthalmology 117:747–56.e4

Bressler NM, Doan QV, Varma R, Lee PP, Suner IJ, Dolan C, Danese MD, Yu E, Tran I, Colman S (2011) Estimated cases of legal blindness and visual impairment avoided using ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. Arch Ophthalmol 129:709–717

Bressler NM, Boyer DS, Williams DF, Butler S, Francom SF, Brown B, Nucci FD, Cramm T, Tuomi LL, Ianchulev T, Rubio RG (2012) Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. Retina 32:1821–1828

Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S, ANCHOR Study Group

(2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355:1432–1444

Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T, ANCHOR Study Group (2009) Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology 116:57–65.e5

Brown D, Heier JS, Chong VNH, Schmidt-Erfurth UM (2011a) One-year results of the VIEW 1 and VIEW 2 studies: VEGF trap-eye in wet AMD. Presented at American Academy of Ophthalmology, Orlando, 24 Oct 2011

Brown DM, Heier JS, Ciulla T, Benz M, Abraham P, Yancopoulos G, Stahl N, Ingerman A, Vitti R, Berliner AJ, Yang K, Nguyen QD, CLEAR-IT 2 Investigators (2011b) Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. Ophthalmology 118:1089–1097

Campbell JP, Bressler SB, Bressler NM (2012) Impact of availability of anti-vascular endothelial growth factor therapy on visual impairment and blindness due to neovascular age-related macular degeneration. Arch Ophthalmol 130:794–795

CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 364: 1897–1908

CATT Research Group, Martin DF, Maguire MG, Fine SL, Ying G, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two year results. Ophthalmology 119:1388–1398

Chakravarthy U (2012) Alternative treatments to Inhibit VEGF in Age-Related choroidal Neovascularization (IVAN): 1 year results. Presented at Association for Research in Vision in Ophthalmology, Fort Lauderdale, 6 May 2012

Chang TS, Bressler NM, Fine JT, Dolan CM, Ward J, Klesert TR, MARINA Study Group (2007) Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. Arch Ophthalmol 125:1460–1469

Data analysis, statistical issues, and data monitoring. In: Comparison of Age-related Macular Degeneration Treatments Trials (CATT). CATT: Lucentis-Avastin trial: manual of procedures. 2010: 10-1–10-14. http://www.med.upenn.edu/cpob/studies/documents/CATTManualofProceduresMay2010_000.pdf

Dave SB, Toma HS, Kim SJ (2011) Ophthalmic antibiotic use and multidrug-resistant staphylococcus epidermidis: a controlled, longitudinal study. Ophthalmology 118:2035–2040

El-Mollayess GM, Noureddine BN, Bashshur ZF (2011) Bevacizumab and neovascular age related macular degeneration: pathogenesis and treatment. Semin Ophthalmol 26:69–76

Ferrara N, Damico L, Shams N, Lowman H, Kim R (2006) Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 26:859–870

Goldberg RA, Flynn HW Jr, Isom RF, Miller D, Gonzalez S (2012) An outbreak of streptococcus endophthalmitis after intravitreal injection of bevacizumab. Am J Ophthalmol 153:204–208.e1

Goodnough A (2012) Sterility found lacking at drug site in outbreak. New York Times. http://www.nytimes.com/2012/10/24/health/sterility-found-lacking-at-drug-site-in-meningitis-outbreak.html?pagewanted=all. Accessed 24 Oct 2012

Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group (2004) Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 351:2805–2816

Green-Simms AE, Ekdawi NS, Bakri SJ (2011) Survey of intravitreal injection techniques among retinal specialists in the United States. Am J Ophthalmol 151: 329–332

Heier JS (2011) VEGF Trap-Eye for AMD: VIEW 1/ VIEW 2 studies. Presented at Retina Subspecialty Day, American Academy of Ophthalmology, Orlando, 22 October 2011

Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U, VIEW 1 and VIEW 2 Study Groups (2012) Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 119:2537–2548

Holz FG, Amoaku W, Donate J, Guymer RH, Kellner U, Schlingemann RO, Weichselberger A, Staurenghi G, SUSTAIN Study Group (2011) Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology 118:663–671

Hsu J (2007) Drug delivery methods for posterior segment disease. Curr Opin Ophthalmol 18:235–239

IVAN Patient Safety Letter (2012) http://cteu.bris.ac.uk/trials/ivan/PatientSafetyLetter.pdf. Accessed 6 Nov 2012

Kaiser PK, Brown DM, Zhang K, Hudson HL, Holz FG, Shapiro H, Schneider S, Acharya NR (2007) Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. Am J Ophthalmol 144:850–857

Kernt M, Thiele S, Neubauer AS, Koenig S, Hirneiss C, Haritoglou C, Ulbig MW, Kampik A (2012) Inhibitory activity of ranibizumab, sorafenib, and pazopanib on light-induced overexpression of platelet-derived growth factor and vascular endothelial growth factor A and the vascular endothelial growth factor A receptors 1 and 2 and neuropilin 1 and 2. Retina 32:1652–1663

Khurana RN, Dupas B, Bressler NM (2010) Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. Ophthalmology 117:1376–1380

Kim AJ, Boylan NJ, Suk JS, Lai SK, Hanes J (2012) Non-degradative intracellular trafficking of highly compacted polymeric DNA nanoparticles. J Control Release 158:102–107

Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, Davis JL, Flynn HW Jr, Esquiabro M (2009) A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 148:43–58.e1

Loewenstein A, Ferencz JR, Lang Y, Yeshurun I, Pollack A, Siegal R, Lifshitz T, Karp J, Roth D, Bronner G, Brown J, Mansour S, Friedman S, Michels M, Johnston R, Rapp M, Havilio M, Rafaeli O, Manor Y (2010) Toward earlier detection of choroidal neovascularization secondary to age-related macular degeneration: multicenter evaluation of a preferential hyperacuity perimeter designed as a home device. Retina 30:1058–1064

Martin TW, Maremont M, Rockoff JD (2012) Tainted drug passed lab test. Wall Street Journal. http://online.wsj.com/article/SB10001424052970204076204578076891268537914.html. Accessed 24 Oct 2012

McCannel CA (2011) Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. Retina 31:654–661

Moshfeghi AA, Rosenfeld PJ, Flynn HW Jr, Schwartz SG, Davis JL, Murray TG, Smiddy WE, Berrocal AM, Dubovy SR, Lee WH, Albini TA, Lalwani GA, Kovach JL, Puliafito CA (2011) Endophthalmitis after intravitreal anti-vascular endothelial growth factor antagonists: a six-year experience at a university referral center. Retina 31:662–668

Moss JM, Sanislo SR, Ta CN (2009) A prospective randomized evaluation of topical gatifloxacin on conjunctival flora in patients undergoing intravitreal injections. Ophthalmology 116:1498–1501

Nguyen QD, Schachar RA, Nduaka CI, Sperling M, Basile AS, Klamerus KJ, Chi-Burris K, Yan E, Paggiarino DA, Rosenblatt I, Khan A, Aitchison R, Erlich SS (2012) Phase 1 dose-escalation study of a siRNA targeting the RTP801 gene in age-related macular degeneration patients. Eye 26:1099–1105

Nussenblatt RB, Byrnes G, Sen HN, Yeh S, Faia L, Meyerle C, Wroblewski K, Li Z, Liu B, Chew E, Sherry PR, Friedman P, Gill F, Ferris F 3rd (2010) A randomized pilot study of systemic immunosuppression in the treatment of age-related macular degeneration with choroidal neovascularization. Retina 30:1579–1587

Patel S (2009) Combination therapy for age-related macular degeneration. Retina 29:S45–S48

Pechan P, Rubin H, Lukason M, Ardinger J, DuFresne E, Hauswirth WW, Wadsworth SC, Scaria A (2009) Novel anti-VEGF chimeric molecules delivered by AAV vectors for inhibition of retinal neovascularization. Gene Ther 16:10–16

Querques G, Querques L, Rafaeli O, Canoui-Poitrine F, Bandello F, Souied EH (2011) Preferential hyperacuity perimeter as a functional tool for monitoring exudative age-related macular degeneration in patients treated by intravitreal ranibizumab. Invest Ophthalmol Vis Sci 52:7012–7018

Ramakrishnan V, Bhaskar V, Law DA, Wong MH, DuBridge RB, Breinberg D, O'Hara C, Powers DB, Liu G, Grove J, Hevezi P, Cass KM, Watson S, Evangelista F, Powers RA, Finck B, Wills M, Caras I, Fang Y, McDonald D, Johnson D, Murray R, Jeffry U (2006) Preclinical evaluation of an anti-alpha5beta1 integrin antibody as a novel anti-angiogenic agent. J Exp Ther Oncol 5:273–286

Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, Shams N (2008) Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 145:239–248

Rich RM, Rosenfeld PJ, Puliafito CA, Dubovy SR, Davis JL, Flynn HW Jr, Gonzalez S, Feuer WJ, Lin RC, Lalwani GA, Nguyen JK, Kumar G (2006) Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 26:495–511

Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, MARINA Study Group (2006) Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355:1419–1431

Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik JF, Schlingemann RO, Axer-Siegel R, Wiedemann P, Simader C, Gekkieva M, Weichselberger A, EXCITE Study Group (2011) Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 118:831–839

Shah CP, Garg SJ, Vander JF, Brown GC, Kaiser RS, Haller JA, Post-Injection Endophthalmitis (PIE) Study Team (2011) Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmology 118:2028–2034

Singer M (2009) HORIZON extension trial of ranibizumab for neovascular age-related macular degeneration: two-year safety and efficacy results. Presented at Association for Research in Vision and Ophthalmology, Fort Lauderdale, 5 May 2009

Spaide RF, Laud K, Fine HF, Klancnik JM Jr, Meyerle CB, Yannuzzi LA, Sorenson J, Slakter J, Fisher YL, Cooney MJ (2006) Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 26:383–390

Speaker MG, Menikoff JA (1991) Prophylaxis of endophthalmitis with topical povidone-iodine. Ophthalmology 98:1769–1775

Steinbrook R (2006) The price of sight – ranibizumab, bevacizumab, and the treatment of macular degeneration. N Engl J Med 355:1409–1412

Suñer I, The HARBOR Study Group (2012) Efficacy and safety of 2 mg or 0.5 mg ranibizumab in patients with

subfoveal neovascular age-related macular degeneration: the HARBOR Study. Presented at Association for Research in Vision and Ophthalmology, Fort Lauderdale, 8 May 2012

The IVAN Study Investigators (2012) Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 119:1399–1411

Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group (1999) Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report. Arch Ophthalmol 117: 1329–1345

U.S. Food and Drug Administration (2004) FDA approves new drug treatment for age-related macular degeneration. http://www.fda.gov/newsevents/newsroom/ pressannouncements/2004/ucm108385.htm. Accessed 25 May 2012

Wang F, Yu S, Liu K, Chen FE, Song Z, Zhang X, Xu X, Sun X (2013) Acute intraocular inflammation caused by endotoxin after intravitreal injection of counterfeit bevacizumab in Shanghai, China. Ophthalmology 120:355–361

Weismann D, Hartvigsen K, Lauer N, Bennett KL, Scholl HP, Charbel Issa P, Cano M, Brandstatter H, Tsimikas S, Skerka C, Superti-Furga G, Handa JT, Zipfel PF, Witztum JL, Binder CJ (2011) Complement factor H binds malondialdehyde epitopes and protects from oxidative stress. Nature 478:76–81

Wykoff CC, Flynn HW Jr, Rosenfeld PJ (2011a) Prophylaxis for endophthalmitis following intravitreal injection: antisepsis and antibiotics. Am J Ophthalmol 152:717–9.e2

Wykoff CC, Flynn HW Jr, Han DP (2011b) Allergy to povidone-iodine and cephalosporins: the clinical dilemma in ophthalmic use. Am J Ophthalmol 151:4–6

Xie B, Shen J, Dong A, Rashid A, Stoller G, Campochiaro PA (2009) Blockade of sphingosine-1-phosphate reduces macrophage influx and retinal and choroidal neovascularization. J Cell Physiol 218:192–198

Yuan A, Kaiser PK (2011) Emerging therapies for the treatment of neovascular age related macular degeneration. Semin Ophthalmol 26:149–155

Zarbin MA, Rosenfeld PJ (2010) Pathway-based therapies for age-related macular degeneration: an integrated survey of emerging treatment alternatives. Retina 30:1350–1367

# Dry Eye Syndrome in the Elderly: Challenges and Treatment Options

9

Fabiana Kimie Kashiwabuchi,
Murilo Wendeborn Rodrigues Jr.,
and Peter J. McDonnell

## 9.1 Introduction

The term dry eye was initially introduced by Roetth in 1953, who described dry eye as low flow of tears measured with the Schirmer test (de Roetth 1953). Now in the twenty-first century, our understanding of the underlying mechanisms and multiple possible etiologies underlying this form of ocular surface disease is more complex and nuanced, but the term "dry eye" is still prevalently used worldwide (Morube 2004).

Dry eye disease (DED) has received different denominations in attempt to better define this condition: keratoconjunctivitis sicca, dry eye syndrome, and dysfunctional tear syndrome (DTS) (Lemp 2008a).

Most recent attempts to define this entity vary from Roetth in that they do not require a reduced flow of tears and are not linked to any particular diagnostic test (such as the Schirmer test). The National Eye Institute, in 1995, defined DED as "disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort" (Lemp 1995).

In a 2007 report of the International Dry Eye Workshop (DEWS), dry eye was defined as a "multi factorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" (Lemp et al. 2007).

## 9.2 Epidemiology

According with World Health Organization (WHO), 650 million people aged 60 years and over are alive today. In 2050 the elderly population is expected to reach two billion, reflecting improvements in nutrition and healthcare in modern societies (WHO 2011). This aging of the world's population portends a dramatically increasing burden of ocular surface disease from dry eye.

Dry eye is a public health problem with major quality of life impact (QOL), frequently associated with social, physical, and psychological disturbance. In addition, it is a chronic disease and usually requires long-term clinical follow up (Friedman 2010).

Many diagnostic tests are currently available in the clinic and used variably in attempts to define DED; however, there is no consensus of which diagnostic test must be employed. Because it is a symptomatic condition, symptoms questionnaires are usually applied as auxiliary instrument to help establish the diagnosis (Smith et al. 2007). These questionnaires can provide significant

F.K. Kashiwabuchi, MD (✉) • M.W. Rodrigues Jr.
P.J. McDonnell
Department of Cornea,
Wilmer Eye Institute, Johns Hopkins Hospital,
Baltimore, MD, USA
e-mail: fabikimie@yahoo.com.br

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_9, © Springer-Verlag Berlin Heidelberg 2013

information, however, may not truly represent the reality of an epidemiologic study because of its subjective aspect (Uchino et al. 2011).

The prevalence of dry eye in the USA among adults aged 50 years and older has been estimated about 3.23 million of women (approximately 7 %) and 1.68 million of men (about 4 %). DED is considered a common condition among women 50 years old and over in USA (Schaumberg et al. 2003, 2009).

According with Koumi study, the high prevalence of DED among Japanese might be related with ethnicity (Uchino et al. 2011), and some studies from Asia suggested higher prevalence among this population. Lin has demonstrated that Taiwanese women are at high risk to develop dry eyes symptoms and positive dry eye tests (Lin et al. 2003).

## 9.3 Risk Factors

Aging is considered the most important risk factor for DED. There are others ophthalmologic comorbidities aging related as cataract, glaucoma, aging macular disease, and diabetic retinopathy (Tsubota et al. 2010).

Consistent factors for dry eye include older age, female sex, and use of hormone replacement therapy, particularly estrogen (Schaumberg et al. 2001), decrease of androgen levels, vitamin A deficiency, malabsorption, and eating disorders are also included as factor risks for DED (Jaworowski et al. 2002; Sullivan et al. 2000).

Some medical conditions and systemic medications have been recognized as risk factor for development of DED. Galor et al. have shown that patients who present with psychiatric illness, autoimmune disease, benign prostatic hyperplasia (BPH), sleep apnea, rosacea, and human immunodeficiency virus are roughly two times more likely to also present with DED (Galor et al. 2011).

Patients taking antihistamines, antianxiety agents, antidepressant, and agents used to manage BPH were also almost two times more expected to develop DED (Galor et al. 2011). Manaviat et al. showed higher prevalence of DED among type 2 diabetic patients with diabetic retinopathy (Manaviat et al. 2008).

The Beaver Dam Eye Study showed that current and past smoking, multivitamin use, and history of heavy alcohol consumption in the past were related with increased risk for DED whereas caffeine consumption was associated with decreased risk (Moss et al. 2000).

### 9.3.1 Patient History

Patient history has a relevant role to establish the diagnosis and appropriate therapy, to identify causes of DED, and to principally relieve patient discomfort and prevent related complications.

A factor which may precipitate and/or exacerbates the symptoms of DED is long-term contact lens wear. Guillon and Maissa showed that tear film evaporation at normal humidity when a patient is wearing contact lenses is similar to evaporation at low humidity in eyes without contact lenses (Guillon and Maissa 2008).

Detailed history of ocular surgeries must be investigated because most surgical procedures which cause cornea denervation may exacerbate preexisting dry eye symptoms, including cataract (Cho and Kim 2009) and refractive surgery, presumably due to damage of corneal nerves during the corneal incision (Albietz et al. 2004). The chronic use of eyedrops containing preservatives can lead to ocular surface damage, as the consequence of allergic reaction and reactions, and direct epithelial damage (Mantelli et al. 2011).

Modern living, including work in indoor air-conditioned environments, computer use, prolonged reading, watching television, and driving appear to negatively impact on DES; hence, it is often helpful to investigate the patient's everyday activities with the goal of possibly alternating environmental stresses (Miljanovic et al. 2007).

### 9.3.2 Secondary Mechanical Conditions

Elderly populations are more susceptible to conditions that can lead to eyelid malpositions or

dysfunction and consequently DED symptoms. Examples of these conditions include involutional entropion and ectropion, loss of inferior eyelid tonicity, nocturnal lagophthalmos, and neurological conditions as Parkinsonism with reduced blink rate and paralysis of cranial nerve VII (Bashour and Harvey 2000). Damasceno et al. showed that entropion is more often associated with DED symptoms and also is more prevalent among women (Damasceno et al. 2011).

Conjunctivochalasis is also a condition increasingly prevalent with age and may result in DED symptoms by aggravating a preexisting DED condition, caused basically by aqueous tear deficiency (Yokoi, et al. 2005).

The recognition of these mechanical conditions is crucial for an effective treatment (Di Pascuale et al. 2004), because once detected and treated, the DED symptoms tend to recover (Henstrom et al. 2011).

## 9.4 Symptoms

Dry eye is considered the most typical cause of chronic eye irritation in patients 50 years and older. The most frequent symptom related is sandy-gritty sensation or burning, which gets worse with the course of the day (Gilbard 2009).

Others symptoms, also frequent, include tearing, blurring vision, and sometimes, redness, mainly when associate with blepharitis. The patient with DED usually refers symptoms intensification after exposition to air-conditioning, wind, prolonged staring, or any situation that causes diminishing of blink rate. Reflex tearing, a paradox symptom, may occur even before establishment of irritated and uncomfortable eyes (Terry 2001).

DED affect directly the QOL and has considerable impact on daily activities and psychological, physical, and social life, especially if the symptoms of dry eye are persistent. However, QOL is an effective tool to evaluate whether the therapy applied was sufficient to improve the symptoms (Friedman 2010).

## 9.5 Etiopathogenesis

One classification scheme divides DED in two major categories: *aqueous tear-deficient dry eye* and *evaporative dry eye*. Mathers and Lane verified a reduction in tear film function with aging; there is a decrease of tear flow and volume and an increase of tear film evaporation and osmolarity (Mathers and Lane 1998).

### 9.5.1 Aqueous Tear-Deficient Dry Eye (ADDE)

ADDE is considered to represent an inefficient lacrimal secretion due dysfunction or destruction of lacrimal gland tissue, reducing tear production and secretion. Consequently to this process, a modification of increased tear osmolarity is believed to occur, and this hyperosmolarity is thought to be responsible for the inflammatory response and subsequent damage to the ocular surface. Furthermore, ADDE also have two subclasses: Sjögren syndrome dry eye and non-Sjögren syndrome dry eye (Lemp et al. 2007).

#### 9.5.1.1 Sjögren Syndrome Dry Eye (SSDE)

Sjögren syndrome is an autoimmune endocrinopathy in which the main targets are lacrimal and salivary glands. There are two ways SSDE becomes manifest: primary (PSS) or secondary (SSS). PSS correspond clinically aqueous-deficient dry eye, associated with reduction of salivary secretion (Zoukhri 2006). Two age peaks are found on PSS, the first, around 20–30 years old and the second, in the mid-50s (Fox 2005). SSS represents the same characteristic of PSS associated with other autoimmune disorders including rheumatoid arthritis and systemic lupus erythematosus (Zoukhri 2006).

#### 9.5.1.2 Non-Sjögren Syndrome Dry Eye (NSSDE)

Non-Sjögren syndrome dry eye is a subdivision of ADDE when systemic autoimmune etiology was discharged. For many years, this entity was considered synonymous with keratoconjunctivitis sicca (KCS). There are different forms of NSSDE,

and they are classified as: primary and secondary lacrimal gland deficiencies, obstruction of the lacrimal gland ducts, and reflex hyposecretion. Age-related dry eye is included in the first classification of primary lacrimal gland deficiencies (Lemp et al. 2007).

### 9.5.2 Evaporative Dry Eye (EDE)

Evaporative dry eye form is characterized by excessive tear evaporation from the ocular surface; however, the lacrimal secretory function is considered normal. There are two different types described: intrinsic and extrinsic. The intrinsic type, as the name suggests, occurs due to an intrinsic dysfunction of the palpebral structures or functions, for example, meibomian gland dysfunction (MGD), low blink rate, and Parkinson disease (Lemp et al. 2007). In MGD an abnormal lipid excretion results in increased tear evaporation rate and consequently evaporative DED. The major prevalence of MGD is age related, mainly thought to relate to decreased androgen levels (Bron and Tiffany 2004). The extrinsic type includes ocular surface disorders (vitamin A deficiency, topical drugs, and preservatives), contact lens wear, and allergic conjunctivitis (Lemp et al. 2007).

## 9.6 Mechanisms of Dry Eye

Two mechanisms are listed as a potential trigger for inducing DED, *hyperosmolarity* and *tear film instability*, and both may have a concomitant contribution to dry eye symptoms.

### 9.6.1 Hyperosmolarity

The main mechanisms of hyperosmolarity are considered to be the reduced aqueous tear flow and/or elevated evaporation rate of tear film. Hyperosmolarity stimulates the inflammatory cascade by increasing expression and production of proinflammatory cytokines and chemokines. After establishment of DED, inflammation becomes cause and consequence of cell damage (Baudouin 2001). Inflammatory cytokines are up-regulated in the dry eye condition, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and MMP-9 (Yoon et al. 2007).

### 9.6.2 Tear Film Instability

A normal superficial lipid layer is thought to stabilize the tear film due to controlling the physiologic evaporation rate. Once both aqueous and mucin layers become thinner, a focal tear breakup can happen because of tear fluid surface tension (Tsubota 1998). During tear film instability, a temporary increase of tear film hyperosmolarity has been noted. Liu et al. demonstrated that corneal nerves can detect changes in osmolarity, and corneal sensory neurons react by increasing tear film osmolarity, causing ocular discomfort (Liu et al. 2009); subsequently the epithelial cells respond with inflammation and apoptosis (Luo et al. 2007).

## 9.7 Diagnosis

A considerable challenge with the diagnosis, severity-grading, and monitoring response to treatment of DED is the absence of a gold standard test for diagnosis (Schein et al. 1997). In addition, patient symptoms are not often in accordance with the clinical signs; some patients may be extremely symptomatic despite modest visible slit lamp findings, while other patients with beginning epithelial breakdown and other worrisome clinical features will describe minimal subjective complains (Nichols et al. 2004).

An appropriate identification of precipitating factors and quantification of disease severity is necessary for an adequate approach to management.

## 9.8 Classification

One report describes four severity levels for DED, without lid margin disease, based on symptoms and signs. Discomfort, severity, and visual disturbance are included in symptoms

and can vary from none or episodic, mild to severe, and constant. The signs include conjunctival injection and staining and corneal staining and can also vary from none/mild to severe (Behrens et al. 2006).

## 9.9 Treatment

Based on patient signs and symptoms, four severity levels are considered to indicate the treatment, and therapeutic options are recommended according with the severity (Pflugfelder et al. 2007). An appropriate range of therapeutic options should be followed in attempt to avoid treatment of patient level one applying therapeutics approaches for level four (Wilson and Stulting 2007).

The treatment of DED may involve four different options: *tear supplementation*, *tear stimulants, tear retention,* and *antiinflammatory therapy*. Avoiding exacerbating factors, dietary modifications, and eyelid hygiene are examples of nonpharmacologic approaches that also must be considered (Lemp 2008b).

For patients with anterior eyelid margin disease, eyelid hygiene and topical antibiotic are indicated. Posterior eyelid margin disease requires warm massage, oral tetracyclines, and topical steroids if necessary (Behrens et al. 2006).

For severity level one (mild disease), counseling and patient education, environmental changes, and artificial tear substitutes are suggested. If level one measures fail to satisfactorily improve the patient, level two therapies are added: antiinflammatory drugs as topical cyclosporine and corticosteroids, nutritional supplements, and secretagogues, and non-pharmacological approach including punctual plugs and moist chamber. Treatment for level three (severe disease) includes tetracyclines, autologous serum, and punctal plugs. Finally, with severity level four "end stage," systemic immunosuppressive and surgical alternatives may be necessary (Wilson and Stulting 2007).

### 9.9.1 Tear Supplementation

Tear substitutes are hypotonic or isotonic buffered solutions with electrolytes, surfactants, and different levels of viscosity; they can provide additional humidity to the ocular surface, improving the lubrication. There are many ocular lubricants available in the USA; they vary in concentration of electrolytes, osmolarity, viscosity, and presence or absence of preservative. The principal advantage of nonpreserved eyedrops is the possibility of frequent administration without toxic effects, found in preservatives preparations (Pflugfelder et al. 2007).

Sodium hyaluronate is a glycosaminoglycan, and that is able to hold large amounts of water and consequently lubricate adjacent structures. Its relatively high viscosity can stabilize the precorneal tear film and maximizes the residence time on eye surface (Snibson et al. 1990; Shimmura et al. 1995). Hyaluronate has viscoelastic properties, humidifies the ocular surface, and has beneficial effect on the cornea and conjunctival epithelium (Aragona et al. 2002).

Tears supplements used outside the USA often contain hyaluronate, but this molecule has not been approved by US Food and Drug Administration (FDA) (Pflugfelder et al. 2007).

Topical lubricants may help improving symptoms and signs; however, there is no evidence that they can improve the underlying pathology and inflammation found in DED (Pflugfelder et al. 2007).

#### 9.9.1.1 Biological Tear Substitutes

Tear factors are known to be indispensable for the maintenance of normal cornea and conjunctival epithelium. Some of them, including epidermal growth factor, vitamin A, transforming growth factor β (TGF-β), cytokines, and fibronectin, can be found in serum. Tsubota et al. evidenced that autologous serum applied as a tear substitute can improve signs and symptoms of DED (Tsubota et al. 1999).

### 9.9.2 Tear Retention

#### 9.9.2.1 Punctal Occlusion

Punctal plugs are commonly employed to slow tear drainage and can improve DED symptoms and signs. Plugs can be placed into upper, lower, or both puncta. Absorbable punctal plugs type

may be made of collagen or a labile polymer and may last for a few days to about 2 weeks, while nonabsorbable plugs made of silicone or hydrophilic acrylic may remain in place unless spontaneously dislocated or removed by a physician. The most common side effect of occlusion is epiphora (Lemp 1994).

Intracanalicular SmartPlug™ (Medennium, Irvine, CA) is a thermosensitive hydrophobic acrylic polymer, solid at room temperature and soft gel at 37 °C, accommodating into canalicular space (Chen and Lee 2007). Kojima et al. evaluated the SmartPlug™ in patients who had previously been treated with conventional plugs, and they showed clinical and symptoms improvement (Kojima et al. 2006). If plugs become located within the canalicular system, they may be difficult to retrieve and may serve as a nidus for inflammation of infection.

Punctal occlusion may promote immediate tear conservation but may also aggravate the ocular surface irritation because the changes in lacrimal tears composition may be toxic to the cornea and conjunctival epithelium. In addition, the concomitant use of preserved artificial tears in patients with punctal occlusion may raise the eye surface inflammation (Roberts et al. 2007).

#### 9.9.2.2 Moisture Chamber Spectacles

With the objective of increase humidity around the eye, small moist sponges may be attached to the side panels of the patients' eyeglasses or swimming goggles can be used. These devices are able to maintain a humidity rate; however, patient adherence may be poor due cosmetic reasons (Tsubota et al. 1994).

#### 9.9.2.3 Contact Lenses

Boston sclera lens is a rigid gas-permeable lens that vaults over the cornea and rests on the sclera. Tear film is retained between lens and eye surface, and it may be useful to promote healing of persistent epithelial defect refractory to other treatments. Advantages of wearing this lens include decrease of ocular pain and photophobia, besides the improvement of vision acuity (Rosenthal and Corteau 2005).

### 9.9.3 Tear Stimulants

Pilocarpine and cevimeline, cholinergic parasympathomimetic agonists' agents, are FDA approved for dry mouth associated with Sjögren syndrome, but not for DED treatment (Lemp 2008a).

A multicenter, double-blind, placebo-controlled trial evaluates the efficacy of pilocarpine tables for Sjögren syndrome patients with dry eye symptoms. Patients who were treated with 5 mg tablets 4 times per day had a significant change comparing with the placebo group. The most frequent adverse reactions were sweating, followed by urinary frequency, flushing, and increased salivation (Vivino et al. 1999).

Ono et al. evaluated the efficacy of cevimeline in patients with Sjögren syndrome and concluded that 20 mg 3 times daily can effectively improve the symptoms related to dryness compared to placebo (Ono et al. 2004).

### 9.9.4 Antiinflammatory

#### 9.9.4.1 Corticosteroids

Corticosteroids (CEs) have been worldwide used to treat a diversity of eye surface inflammation, because of their cytokines inhibition capacity. De paiva et al. showed that 1 % methylprednisolone, a very potent CE, can preserve apical corneal barrier function and can promote a great clinical improvement (de Paiva et al. 2006; Pflugfelder et al. 2007). Nonpreserved 1 % methylprednisolone solution had a remarkable improvement in ocular irritation symptoms. Marsh and Pflugfelder evaluated the efficacy and side effects of topical methylprednisolone and found that this CE is an effective treatment option for patients with severe DED secondary to Sjögren syndrome (Marsh and Pflugfelder 1999).

Due the reduced intraocular effect and/or penetration of "soft steroids" such as fluorometholone and loteprednol etabonate, they might be unlikely to modify the intraocular pressure IOP (de Paiva and Pflugfelder 2008). Pflugfelder et al. performed a study evaluating loteprednol etabonate ophthalmic 0.5 % suspension for treatment of DED in

patients with moderate inflammatory component; after 4 weeks of treatment no elevation of IOP was observed (Pflugfelder et al. 2007).

Although topical CEs for DED have been shown to be of benefit, their long-term use may stimulate cataract formation, glaucoma, and ocular infection. For this reason, CE should be used for short-term periods, during disease exacerbations (Pflugfelder et al. 2007).

#### 9.9.4.2 Topical Cyclosporine

Cyclosporine, an immunomodulatory drug, is considered the second most common drug, followed by CEs, used in treatment of immune-mediated ocular surface illness. Currently, it is the only pharmacologic treatment FDA approved particularly for DED that aims to normalize tear composition and production (Lemp 2008a).

The efficacy, safety, and patient tolerability of this drug have been demonstrated for assorted eye surface disorders (Utine et al. 2010; Foulks 2006). Yüksel evaluated the efficacy of topical cyclosporine by clinical and cytologic methods in patients with DED and demonstrated that after 6 month of therapy, severe dry eye patients had no satisfactory response as mild to moderate severity patients had (Yüksel et al. 2010).

#### 9.9.4.3 Tetracyclines

Tetracyclines and derivatives have both antiinflammatory and antibacterial properties. Oral tetracyclines have been used off-label to DED treatment (Lemp 2008a).

Doxycycline is a therapeutic agent FDA approved for inflammatory skin lesions of rosacea, however, not for ocular rosacea (Lemp 2008a). The main action of doxycycline in patients with rosacea may be the capacity that this drug has to inhibit angiogenesis (de Paiva and Pflugfelder 2008).

Clinical reports propose that doxycycline has a successful effect in the treatment of inflammatory ocular diseases due its capacity of decrease collagenase, phospholipase A2 activity, and inhibition of proinflammatory cytokines (Smith and Cook 2004; de Paiva and Pflugfelder 2008).

Shine et al. suggested that minocycline may reduce inflammation reaction by decreasing meibomian gland lipid degradation products and consequently decrease neutrophil recruitment (Shine et al. 2003).

Yoo et al. verified improvements in dry eye symptoms after ingestion of doxycycline in patients with chronic meibomian dysfunction, who had performed the conventional therapy including warm eyelid massage and topical antibiotic therapy, with no success (Yoo et al. 2005).

#### 9.9.4.4 Essencial Fatty Acids

Essential fatty acids are considered potential modulator of inflammatory activity and must be taken from food. Miljanovic et al. demonstrated a reduction of prevalence of DED among women with a higher consumption of n-3 fatty acids than those with lowest intake (Miljanovic et al. 2005).

Barabino et al. verified that systemic linoleic and gamma-linolenic acid administered twice a day has an antiinflammatory activity in patients with DED, with improvement of ocular irritation (Barabino et al. 2003). A study performed by Aragona et al. showed increase of prostaglandin (PGE1), which has antiinflammatory properties, and improvement of symptoms of ocular discomfort and signs of corneal epithelial defects (Aragona et al. 2005).

### 9.9.5 Potential Dry Eye Treatment

There are some potential options for DED treatment that are in various stages of phase II and III clinical trials. Promising results have been shown, and new treatment alternatives may help alleviate DED symptom.

#### 9.9.5.1 SAR 1118

The SAR 1118 ophthalmic solution (SAR-code Bioscience, Brisbane, Calif) has the property of inhibiting T-cell-mediated inflammation acting on cellular surface proteins. The phase II trial was a randomized, placebo-controlled, multicenter study. SAR 1118 was reported to be well tolerated, with improvement in corneal staining and significant increase in tear production (Semba et al. 2012). Currently, SAR 1118 is in phase III trials.

#### 9.9.5.2 CF101

CF101 is an adenosine receptor agonist, shown in preclinical and clinical studies to have antiinflammatory effect. In at phase II study, CF101 was administrated orally, as monotherapy for 12 weeks, by patients with moderate to severe dry eye. The drug was reportedly well tolerated and safe, without serious adverse events (Avni et al. 2010). Currently, the drug is in phase III clinical trial.

#### 9.9.5.3 Dexamethasone Phosphate (EGP-437)

A single center, double-masked, randomized, placebo phase II trial evaluated ocular iontophoresis of EGP-437 (40 mg/mL) in patients with moderate to severe DED. Iontophoresis is a drug delivery technique which applies electrical field at ocular surface with the purpose of propelling charged drug, increasing ocular drug concentration. The results showed improvement of symptoms of dryness over 3-week study period relative to placebo (Patane et al. 2011).

#### 9.9.5.4 Bromfenac

Bromfenac is a nonsteroidal antiinflammatory drug being evaluated as a potential therapy for DED.

#### 9.9.5.5 Acupuncture

The Korea Institute of Oriental Medicine has completed a phase III trial. The purpose of this study was to verify if acupuncture is more effective than artificial tears for treatment of DED. In one group, seventeen acupuncture points were selected and acupuncture needles were placed on these points. The other group received preservative-free lubricant once a day for 4 weeks. Results have not yet been published.

## 9.10 Management Challenges

Aging populations are more susceptible to manifest visual impairment. Both DED and glaucoma are chronic conditions that require long-term care compliance with topical drop administration. Prolonged use of eyedrops containing preservatives can increase tear evaporation with subsequent discomfort (Rossi et al. 2009).

According with Department of Health and Human Services, in 2008, 68 % of the adult incident cases of diabetes were diagnosed between 40 and 64 years old and 17 % at age 65 or older (Department of Health and Human Services 2010).

Diabetes itself may decrease corneal sensation due peripheral neuropathy and also reduced tear secretion. Dogru et al. showed considerable changes in tear function and impression cytologic parameters in diabetic patients. Furthermore, fluctuations in glycemic levels may change the lacrimal gland function (Dogru et al. 2001).

Niti et al. demonstrate depression in 13.3 % of population aged 55 and older. There is a connection between depression and chronic diseases, principally if the chronic illness can cause any functional incapacitation (Niti et al. 2007).

Managing patients with dry eye associated with depression might be harder to quantify because these group may overestimate their symptoms and not believe that treatment will improve the symptoms, leading to noncompliance. Studies have shown depressive symptoms among older populations principally caused by physical disorder and functional disability (Lépine and Bouchez 1998). The psychological disturbance may be caused because of eye discomfort, disappointment with treatment results, and diminished QOL (Li et al. 2011).

Burns and Mulley demonstrated that practical issues were frequent among elderly patients, and they presented difficulties in self-application medication. The main difficulty seems to be the capability of the patient to precisely place the medication on the eye (Burns and Mulley 1992). Winfield et al. evaluated patient problems during self-medication with eyedrops, and they verified that 14 % had difficulties with reading labels and identifying bottle, 13 % poor visibility of tip of dropper, and 8 % with shaky hands (Winfield et al. 1990).

Some others age-related factors have a relevant influence in noncompliance to medication as decrease quality of vision, hearing, and memory; reduced cognitive and physical functions; and limited social and financial funds (Murray et al. 2004).

**Acknowledgments** Conflict of Interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Albietz JM, Lenton LM, McLennan SG (2004) Chronic dry eye and regression after laser in situ keratomileusis for myopia. J Cataract Refract Surg 30:675–684

Aragona P, Papa V, Micali A et al (2002) Long term treatment with sodium hyaluronate containing artificial tears reduces ocular surface damage in patients with dry eye. Br J Ophthalmol 86:181–184

Aragona P, Bucolo C, Spinella R et al (2005) Systemic oomega-6 essential fatty acid treatment and PGE1 tear content in Sjögren's syndrome patients. Invest Ophthalmol Vis Sci 46:4474–4479

Avni I, Garzozi HJ, Barequet IS et al (2010) Treatment of dry eye syndrome with orally administered CF101-data from a phase 2 clinical trial. Ophthalmology 117:1287–1293

Barabino S, Rolando M, Camicione P et al (2003) Systemic linoleic and γ-linolenic acid therapy in dry eye syndrome with an inflammatory component. Cornea 22:97–101

Bashour M, Harvey J (2000) Causes of involutional ectropion and entropion- age related tarsal changes are the key. Ophthal Plast Reconstr Surg 16:131–141

Baudouin C (2001) The pathology of dry eye. Surv Ophthalmol 45:S211–S220

Behrens A, Doyle JJ, Stern L et al (2006) Dysfunctional tear syndrome- a Delphi approach to treatment recommendations. Cornea 25:900–907

Bron AJ, Tiffany JM (2004) The contribution of meibomian disease to dry eye. Ocul Surf 2:149–164

Burns E, Mulley GP (1992) Practical problems with eyedrops among elderly ophthalmology outpatients. Age Ageing 21:168–170

Chen SX, Lee GA (2007) SmartPlug in the management of severe dry eye syndrome. Cornea 26:534–538

Cho YK, Kim MS (2009) Dry eye after cataract surgery and associated intraoperative risk factors. Korean J Ophthalmol 23:65–73

Damasceno RW, Osaki MH, Dantas PEC et al (2011) Involutional entropion and ectropion of the lower eyelid: prevalence and associated risk factors in the elderly population. Ophthal Plast Reconstr Surg 27: 317–320

de Paiva CS, Pflugfelder SC (2008) Rationale for anti-inflammatory therapy in dry eye syndrome. Arq Bras Oftalmol 71:S89–S95

de Paiva CS, Corrales RM, Villarreal AL (2006) Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. Exp Eye Res 83:526s–535s

de Roetth AFM (1953) Low flow of tears- the dry eye. Am J Ophthalmol 35:782–787

Department of Health and Human Services (2010) Distribution of age at diagnosis of diabetes among adult incident cases aged 18–79 years, United States, 2008. http://www.cdc.gov.proxy3.library.jhu.edu/diabetes/statistics/age/fig 1.htm. Accessed 6 Dec 2011

Di Pascuale MA, Espana EM, Kawakita T et al (2004) Clinical characteristics of conjunctivochalasis with or without aqueous tear deficiency. Br J Ophthalmol 88:388–392

Dogru M, Katakami C, Inoue M (2001) Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology 108:586–592

Foulks GN (2006) Topical cyclosporine for treatment of ocular surface Disease. Int Ophthalmol Clin 46: 105–122

Fox RI (2005) Sjögren's syndrome. Lancet 366:321–331

Friedman NJ (2010) Impact of dry eye disease and treatment on quality of life. Curr Opin Ophthalmol 21:310–316

Galor A, Feuer W, Lee DJ et al (2011) Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. Am J Ophthalmol 152: 377–384

Gilbard JP (2009) Dry eye blepharitis: approaching the patient with chronic eye irritation. Geriatrics 6: 22–26

Guillon M, Maissa C (2008) Contact lens wear affects tear film evaporation. Eye Contact Lens 34:326–330

Henstrom DK, Lindsay RW, Cheney ML et al (2011) Surgical treatment of the periocular complex and improvement of quality of life in patients with facial paralysis. Arch Facial Plast Surg 13:125–128

Jaworowski S, Drabkin E, Rozenman Y (2002) Xerophthalmia and undiagnosed eating disorder. Psychosomatics 43:506–507

Kojima T, Dogru M, Ishida R et al (2006) Clinical evaluation of the SmartPlug TM in the treatment of dry eyes. Am J Ophthalmol 141:386–387

Lemp MA (1994) Management of the dry-eye patient. Int Ophthalmol Clin 34:101–113

Lemp MA (1995) Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry eyes. CLAO J 21:221–232

Lemp MA (2008a) Advances in understanding and managing dry eye disease. Am J Ophthalmol 146: 350–356

Lemp MA (2008b) Management of dry eye disease. Am J Manag Care 14:S88–S101

Lemp MA, Baudouin C, Baum J et al (2007) The definition and classification of dry eye disease: report of Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 5:75–92

Lépine JP, Bouchez S (1998) Epidemiology of depression in the elderly. Int Clin Psychopharmacol 13:S7–S12

Li M, Gong L, Sun X et al (2011) Anxiety and depression in patients with dry eye syndrome. Curr Eye Res 36:1–7

Lin PY, Tsai SY, Cheng CY et al (2003) Prevalence of dry eye among an elderly Chinese population in

Taiwan- the Shihpai Eye Study. Ophthalmology 110: 1096–1101
Liu H, Begley C, Chen M et al (2009) A link between tear instability and hyperosmolarity in dry eye. Arch Ophthalmol 127:763–768
Luo L, Li D, Pflugfelder SC (2007) Hyperosmolarity-induced apoptosis in human corneal epithelial cells is mediated by cytochrome c and MAPK pathways. Cornea 26:452–460
Manaviat MR, Rashidi M, Afkahami-Ardekani M et al (2008) Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. BMC Ophthalmol 8(10)
Mantelli F, Tranchina L, Lambiase A et al (2011) Ocular surface damage by ophthalmic compounds. Curr Opin Allergy Clin Immunol 11:464–470
Marsh P, Pflugfelder SC (1999) Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. Ophthalmology 106: 811–816
Mathers WA, Lane JA (1998) Meibomian gland lipids, evaporation and tear film stability. Adv Exp Med Biol 438:349–360
Miljanovic B, Trivedi KA, Dana MR et al (2005) Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr 82:887–893
Miljanovic B, Dana R, Sullivan DA et al (2007) Impact of dry eye syndrome on vision-related quality of life. Am J Ophthalmol 143:409–415
Morube J (2004) Andrew de Roetth (1893–1981): dacryologist who introduced the term dry eye. Ocul Surf 2:225–227
Moss SE, Klein R, Klein BEK (2000) Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol 118:1264–1268
Murray MD, Morrow DG, Weiner M et al (2004) A conceptual framework to study medication adherence in older adults. Am J Geriatr Pharmacother 2:36–43
Nichols KK, Nichols JJ, Mitchell GL (2004) The lack of association between signs and symptoms patients with dry eye disease. Cornea 23:762–770
Niti M, Ng TP, Kua EH et al (2007) Depression and chronic medical illnesses in Asian older adults: the role of subjective health and functional status. Int J Geriatr Psychiatry 22:1087–1094
Ono M, Takamura E, Shinozaki K et al (2004) Therapeutic effect of cevimeline on dry eye in patients with Sjögren's syndrome: a randomized, double-blind clinical study. Am J Ophthalmol 138:6–17
Patane MA, Cohen A, From S et al (2011) Ocular iontophoresis of EGP-437 (dexamethasone phosphate) in dry eye patients: results of a randomized clinical trial. Clin Ophthalmol 5:633–643
Pflugfelder SC, Maskin SL, Anderson B et al (2007) A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5 %, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. Am J Ophthalmol 138:444–457
Pflugfelder SC, Geerling G, Kinoshita S et al (2007) Management and therapy of dry eye disease: Report of the management and therapy subcommittee of the international dry eye workshop. Ocular surface 5:163–178
Roberts CW, Carniglia PE, Brazzo BG (2007) Comparison of topical cyclosporine, punctual occlusion, and a combination for the treatment of dry eye. Cornea 26:805–809
Rosenthal P, Corteau A (2005) Fluid-ventilated, gas-permeable sclera contact lens is an effective option for managing severe ocular surface disease and many corneal disorders that would otherwise require penetrating keratoplasty. Eye Contact Lens 31:130–134
Rossi GCM, Tinelli C, Pasinetti GM et al (2009) Dry eye syndrome-related quality of life in glaucoma patients. Eur J Ophthalmol 19:572–579
Schaumberg DA, Buring JE, Sullivan DA et al (2001) Hormone replacement therapy and dry eye syndrome. JAMA 286:2114–2119
Schaumberg DA, Sullivan DA, Buring JE et al (2003) Prevalence of dry eye syndrome among US women. Am J Ophthalmol 136:318–326
Schaumberg DA, Dana R, Buring JE et al (2009) Prevalence of dry eye disease among US men. Arch Ophthalmol 127:763–768
Schein OD, Tielsch JM, Munoz B et al (1997) Relation between signs and symptoms of dry eye in the elderly-a population-based perspective. Ophthalmology 104:1395–1401
Semba CP, Torkildsen GL, Lonsdale JD et al (2012) A phase 2 randomized, double-masked, placebo-controlled study of a novel integrin antagonist SAR 1118 for the treatment of dry eye. Am J Ophthalmol 153:1050–1060
Shimmura S, Ono M, Shinozaki K et al (1995) Sodium hyaluronate eyedrops in the treatment of dry eyes. Br J Ophthalmol 79:1007–1011
Shine WE, McCulley JP, Pandya AG (2003) Minocycline effect on meibomian gland lipids in meibomianitis patients. Exp Eye Res 76:417–420
Smith VA, Cook SD (2004) Doxycycline- a role in ocular surface repair. Br J Ophthalmol 88:619–625
Smith JA, Albeitz J, Begley C et al (2007) The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop. Ocul Surf 5:93–107
Snibson GR, Greaves JL, Soper NDW et al (1990) Precorneal residence times of sodium hyaluronate solutions studied by quantitative gamma scintigraphy. Eye 4:594–602
Sullivan DA, Sullivan BD, Ullman MD et al (2000) Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci 41:3732–3741
Terry MA (2001) Dry eye in the elderly. Drugs Aging 18:101–107

Tsubota K (1998) Tear dynamics and dry eye. Prog Retin Eye Res 17:565–596

Tsubota K, Yamada M, Urayama K (1994) Spectacle side panels and moist inserts for the treatment of dry-eye patients. Cornea 13:197–201

Tsubota K, Goto E, Fujita H et al (1999) Treatment of dry eye by autologous serum application in Sjögren's syndrome. Br J Ophthalmol 83:390–395

Tsubota K, Kawashima M, Inaba T et al (2010) The era of antiaging ophthalmology comes of age: antiaging approach for dry eye treatment. Ophthalmic Res 44:146–154

Uchino M, Nishiwaki Y, Michikawa T et al (2011) Prevalence and risk factors of dry eye disease in Japan: Koumi study. Ophthalmology. doi:10.1016/j.ophtha.2011.05.029

Utine CA, Stern M, Akpek EK (2010) Clinical review: topical ophthalmic use of cyclosporine A. Ocul Immunol Inflamm 18:352–361

Vivino FB, Al-Hashimi I, Khan Z et al (1999) Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome. Arch Intern Med 159:174–181

Wilson SE, Stulting RD (2007) Agreement of physician treatment practices with the international task force guidelines for diagnosis and treatment of dry eye disease. Cornea 26:284–289

Winfield AJ, Jessiman D, Williams A et al (1990) A study of the causes of non-compliance by patients prescribed eyedrops. Br J Ophthalmol 74:477–480

World Health Organization (WHO) (2011) 10 facts on ageing and the life course. http://www.who.int/features/factfiles/ageing/en/index.html. Accessed 3 Nov 2011

Yokoi N, Komuro A, Nishii M et al (2005) Clinical impact of conjunctivochalasis on the ocular surface. Cornea 24:S24–S31

Yoo SE, Lee DC, Chang MH (2005) The effect of low dose doxycycline therapy in chronic meibomian gland dysfunction. Korean J Ophthalmol 19:258–263

Yoon KC, Jeong IY, Park YG et al (2007) Interleukin-6 and tumor necrosis factor-α levels in tears of patients with dry eye syndrome. Cornea 26:431–437

Yüksel B, Bozdag B, Acar M et al (2010) Evaluation of the effect of topical cyclosporine A with impression cytology in dry eye patients. Eur J Ophthalmol 20:675–679

Zoukhri D (2006) Effect of inflammation on lacrimal gland function. Exp Eye Res 82:885–898

# Part IV

# The Impact of Visual Disability on Daily Life in Older Populations

# Cataract and Diabetic Retinopathy: Impact on Quality of Life

10

Ecosse L. Lamoureux, Eva Fenwick, and Konrad Pesudovs

## 10.1 Introduction

This chapter explores the impact of two distinctive ocular conditions, cataract and diabetic retinopathy, and their treatment interventions from the patient's perspective. We focus on visual functioning, namely, daily activities such as reading, driving etc., as well as the more holistic concept of vision-specific quality of life (VSQoL) which encompasses aspects beyond functioning including emotional well-being, concerns, social interaction, convenience and work. Both conditions may cause severe visual impairment in their late stages which can considerably affect patients' ability to perform and participate in day-to-day tasks and substantially affect their overall QoL. Cataract is largely reversible due to surgical advances in treatment, and patients tend to report impressive functioning and quality of life (QoL) gains following cataract surgery. Diabetic retinopathy, in contrast, is an irreversible condition with traditional treatment interventions such as laser photocoagulation therapy focussed more on prevention of further visual loss through repeated sessions than restoration of sight. Consequently, the QoL impact of diabetic retinopathy before, during and after treatment interventions remains substantial, although emerging treatments such as anti-vascular endothelial growth factor (VEGF) intraocular injections have shown promise in improving patients' visual acuity and subsequent VSQoL (Mitchell et al. 2011; Loftus et al. 2011). This chapter draws on our combined expertise in the field of patient-reported outcomes and discusses the impact of these two conditions and their associated treatments on functioning and VSQoL while highlighting some of the remaining uncertainties.

E.L. Lamoureux (✉)
Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, VIC, Australia

Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
e-mail: ecosse@unimelb.edu.au

E. Fenwick
Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, VIC, Australia

K. Pesudovs
NHMRC Centre for Clinical Eye Research, Discipline of Optometry and Vision Science, Flinders Medical Centre and Flinders University of South Australia, Adelaide, Australia

## 10.2 Impact of Cataract and Cataract Surgery on Quality of Life

### 10.2.1 Introduction

Cataract is an eye condition that involves the opacification of the natural lens of the eye. Globally, cataract is the single most important cause of blindness with almost 18 million people estimated to be bilaterally blind from cataract,

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_10, 

representing almost half of all causes of blindness due to eye diseases worldwide (Resinkoff et al. 2004). In developing countries, cataract contributes to more than 90 % of the total disability adjusted life years (Rao et al. 2011). With the rapidly ageing population, it seems likely that cataract will continue to have an enormous impact (Rao et al. 2011). Patients with cataract may experience a range of visual deficits such as deterioration in visual acuity, loss of contrast sensitivity, problems under glare conditions and altered colour recognition (Crabtree et al. 1999). These visual deficits lead to a range of real world difficulties and a reduction in QoL (Lamoureux et al. 2011). Cataract is easily treatable due to the availability of safe and effective surgical procedures and advances in intraocular lens design, and cataract surgery is highly successful in reversing visual impairment associated with cataract.

The need for patient-reported information about the impact of cataract leads to the realm of 'Patient-Reported Outcomes (PROs)', an umbrella concept covering a broad range of patient-reported data and measures. Over the last three decades, over 100 PROs have been used to assess the impact of cataract and cataract surgery on generic health, visual functioning (VF) and VSQoL. While these types of outcomes (often referred to as traits) are often used interchangeably in the literature, they have important differences. Generic health refers to overall health status and is non-condition specific. The short-form (SF)-12 and SF-36 are classic examples of instruments developed to assess generic health (Ware and Sherbourne 1992; Ware et al. 1996). VF is assessed with a vision-specific instrument which explores visual disability or vision-related activity limitation. It involves vision-dependent tasks such as reading, driving and shopping. One of the most widely used instruments (also referred as questionnaires, scales or tools) to assess the impact of cataract surgery on VFis the Visual Functioning Index-14 (VF-14) (Steinberg et al. 1994a). Finally, VSQoL is a complex construct that encompasses disability, symptoms, emotional well-being, social relationships, concerns and convenience as they are affected by vision (WHOQOL Group 1997). For example, the Impact of Visual Impairment (IVI) questionnaire, although not holistically a QoL instrument, was designed to provide components of VSQoL beyond functioning and contains eight items assessing vision-specific emotional well-being (Lamoureux et al. 2007a).

### 10.2.2 Impact of Cataract on Visual Functioning and Quality of Life

The presence of cataract has a number of important consequences for patients, including decreased participation in social activities or daily tasks, depression, increased likelihood of admission to a nursing home, increased number of falls (and resultant hip fractures) and increased mortality (McCarty et al. 2001; Wang et al. 2003; Lamoureux et al. 2004a; Klein et al. 1998). Cataract has also been demonstrated to cause significant reductions in patients' VF, VSQoL and health-related QoL (Nanayakkara 2009; Polack et al. 2008, 2010). This patient-centred impact is comparable to that of major systemic conditions including stroke, diabetes and arthritis (Chia et al. 2004).

While a relationship between cataract and poor VF clearly exists, the extent of this association remains relatively unexplored. Recent research has assessed whether the impact of cataract on VF varies according to the type and grade of cataract (Chew et al. 2012). The presence of bilateral but not unilateral cataract was found to be significantly associated with poorer VF after controlling for a range of potential confounders. The impact of cataract on VF was found to be dependent on vision but independent of undercorrected refractive error. Importantly, combinations of cataract types also had greater impact than a single cataract type on VF. A combination of three cataract types resulted in the poorest VF, followed by a combination of two cataract types, and lastly, a single type. Individually, posterior subcapsular cataract had the greatest impact ahead of

nuclear and then cortical cataract. These findings indicate that the effects of the different cataract types are additive and should be taken into consideration when trying to determine the level of VF in a person with cataract.

The association of different types of cataract to VF also appears to vary according to the different grades of cataract (Chew et al. 2012). For example, nuclear cataract is significantly associated with VF from an opalescence grade of at least 4 or a colour grade of at least 5. Likewise, cortical cataract has been shown to be significant upwards from grade 3 only. These findings suggest that visual acuity is the main contributing factor in determining the impact of cataract on VF. Posterior subcapsular cataract occurs centrally and impairs central vision even at an early stage, while cortical cataract only involves the central axis at higher grading levels. Although nuclear cataract is considered significant in Lens Opacities Classification System (LOCS) at the same grade level for 'opalescence' and 'colour', its impact on VF occurs only at a higher grade for 'nuclear colour' (Chew et al. 2012). These findings suggest that a patient's ability to perform vision-dependent tasks may vary according to the different subtypes and grades of their cataract, which supports the need for individualised assessment and management. While these findings are important, further research in other populations is needed.

### 10.2.3 Impact of Cataract Surgery on Patient-Reported Outcomes

Cataract surgery is one of the most cost-effective health-care interventions (Lansingh et al. 2007). It increases time spent on productive activities and reduces time in inactivity and assistance among older adults in low-income settings (Polack et al. 2010). Most age-related cataract cannot be prevented, but cataract surgery is highly effective, resulting in almost immediate visual rehabilitation (Allen 2008). Although assessing the clinical effectiveness of cataract surgery is important, it is also important to understand the impact from the patients perspective as treatment outcomes can sometimes be specific to patients and not necessarily detectable by the treating surgeon.

Many studies have investigated the impact of cataract surgery on PROs (Table 10.1). The most commonly used instrument has been the original VF-14 (Alonso et al. 1997; Amesbury et al. 2009; Bilbao et al. 2009; Browne et al. 2008; Cassard et al. 1995; Damiano et al. 1995; Desai et al. 1996; Espallargues and Alonso 1998; Friedman et al. 2002; Mozaffarieh et al. 2004; Norregaard 2007; Norregaard et al. 2003; Owsley et al. 2007; Pager et al. 2004; Rosen et al. 2005; Saw et al. 2002; Steinberg et al. 1994b; Walker et al. 2006; Lundqvist and Monestam 2006, 2009; Pager 2004) or revised versions (Pager 2004; Uusitalo et al. 1999; Tielsch et al. 1995). The VF-14 was developed and validated for use in cataract populations, and it contains 14 items relating to activities of daily living and functioning, such as reading, writing, driving and negotiating steps. Studies using the VF-14 have generally reported clinically important significant improvements in VF following cataract surgery (Amesbury et al. 2009; Bilbao et al. 2009; Owsley et al. 2007; Walker et al. 2006).

Cataract surgery also unequivocally improves VSQoL (Desai et al. 1996; Owsley et al. 2007; Steinberg et al. 1994b; Donovan et al. 2003; He et al. 1999; Pokharel et al. 1998; Fletcher et al. 1997; Mamidipudi et al. 2003; Liu et al. 2004; Taylor et al. 2008; Zhao et al. 1998) in the areas of self-care, mobility, social interaction, adaptation and coping, and mental and emotional well-being. For instance, large gains in QoL scores after cataract surgery have been found using Ellwein's QoL instrument (Mamidipudi et al. 2003; Liu et al. 2004), the Nursing Home Vision-Targeted QoL instrument (Owsley et al. 2007) and the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) (Kaplan et al. 2010). As shown in Table 10.2, the magnitude of the gains in VF and VSQoL parameters have been substantial with large effect size values recorded in most studies. However, the gains are less striking

**Table 10.1** Summary of studies using first generation instruments assessing the impact of cataract surgery on visual functioning (VF); vision-specific QoL (VSQoL); and generic health-related QoL (HRQoL), with and without other ocular co-morbidities

| | Outcome | Improvement | Limited improvement | No improvement |
|---|---|---|---|---|
| No ocular co-morbidity | VF | VF-14 (Alonso et al. 1997; Amesbury et al. 2009; Bilbao et al. 2009; Browne et al. 2008; Cassard et al. 1995; Damiano et al. 1995; Desai et al. 1996; Espallargues and Alonso 1998; Friedman et al. 2002; Mozaffarieh et al. 2004; Norregaard 2007; Norregaard et al. 2003; Owsley et al. 2007; Pager et al. 2004; Rosen et al. 2005; Saw et al. 2002; Steinberg et al. 1994b; Walker et al. 2006; Lundqvist and Monestam 2006, 2009; Pager 2004; Yuen et al. 2011) | Catquest (Lundstrom and Wendel 2005) | CSS (Owsley et al. 2007) |
| | | ADVS (Mangione et al. 1994; McGwin et al. 2003; Superstein et al. 1999)<br>Catquest (Lundstrom et al. 2000a)<br>CSS (Espallargues and Alonso 1998)<br>TyPE (Javitt et al. 2003)<br>VF-7a (Uusitalo et al. 1999)<br>VF-7b (Pager 2004)<br>VDA (Pesudovs et al. 2003)<br>HVAT (Prager et al. 2000)<br>VF-12 (Tielsch et al. 1995) | VFA (Bassett et al. 2005)<br>MFI (Chang-Godinich et al. 1999) | Catquest (Lundstrom et al. 2000b) |
| | VSQoL | Ellwein's instrument (Fletcher et al. 1997; Mamidipudi et al. 2003; Liu et al. 2004; Yuen et al. 2011)<br>VR-SIP (Desai et al. 1996)<br>VSQ (Donovan et al. 2003)<br>NHVSQoL (Owsley et al. 2007)<br>NEI-VFQ (Kaplan et al. 2010) | Ellwein's instrument (He et al. 1999; Pokharel et al. 1998)<br>VR-SIP (Steinberg et al. 1994b) | Ellwein's instrument (Taylor et al. 2008; Zhao et al. 1998) |
| | Generic HRQoL | Cantril ladder (Pesudovs et al. 2003) | SIP (Cassard et al. 1995; Desai et al. 1996; Espallargues and Alonso 1998) | SIP (Damiano et al. 1995; Steinberg et al. 1994b) |
| | | EQ-5D (Browne et al. 2008; Jayamanne et al. 1999) | SF-36 (Mangione et al. 1994; Chandrasekaran et al. 2008)<br>POMS (Pesudovs et al. 2003)<br>QWB-SA (Rosen et al. 2005; Kaplan et al. 2010)<br>EQ-5D (Kaplan et al. 2010)<br>HUI2 (Kaplan et al. 2010)<br>HUI3 (Kaplan et al. 2010) | SF-36 (Bilbao et al. 2009; Pager et al. 2004)<br>PSMS (Marx et al. 1995)<br>NEADL (Gray et al. 2006)<br>SF-6D (Kaplan et al. 2010) |

| | | | | |
|---|---|---|---|---|
| With ocular co-morbidity (VF only) | AMD | VF-14 (Armbrecht et al. 2003)<br>Catquest (Lundstrom et al. 2002)<br>DLTV (El Mallah et al. 2001) | (mild or moderate AMD)VF-14 (Armbrecht et al. 2000) | |
| | Diabetic retinopathy | | (mild NPDR) VF-14 (Mozaffarieh et al. 2004, 2005, 2009) | |
| | Glaucoma | VAQ (Musch et al. 2006) | | |

*AMD* age-related macular degeneration, *ADVS* Activities of Daily Vision Scale, *CSS* Cataract Symptom Scale, *DLTV* daily living tasks dependent on vision, *EQ-5D* EuroQol-5D, *HRQoL* health-related quality of life, *HUI2* Health Utilities Index Mach 2, *HUI3* Health Utilities Index Mach 3, *HVAT* Houston Vision Assessment Test, *MFI* Mean Functional Impairment, *NEADL* Nottingham Extended Activities of Daily Living, *NEI-VFQ* National Eye Institute's Visual Function Questionnaire, *NHVSQoL* Nursing Home Vision-Targeted Health-Related QoL, *NPDR* nonproliferative diabetic retinopathy, *POMS* Profile of Mood States, *PSMS* Physical Self-Maintenance Scale, QWB-*SA* Quality of Well-Being Scale, *SF-6D* short form-6D, *SIP* Sickness Impact Profile, *VAQ* Visual Activities Questionnaire, *VDA* Visual Disability Assessment, *VFA* Vision Function Assessment, *VSQoL* vision-specific quality of life, *VR-SIP* Vision-Related Sickness Impact Profile, *VSQ* Visual Symptoms and Quality of Life Questionnaire

**Table 10.2** Randomly selected studies showing mean ± SD (standard deviation) pre- and post-cataract VF and QoL values

| | | Preoperation Mean ± SD | Postoperation Mean ± SD | Effect size Cohen's d |
|---|---|---|---|---|
| Owsley et al. (2007) | VF-14 | 68.7 ± 23.5 | 93.6 ± 14.2 | 1.28 |
| Bilbao et al. (2009) | VF-14 | 60.99 ± 22.49 | 85.11 ± 18.10 | 1.18 |
| Walker et al. (2006) | VF-14 | 71.60 ± 16.09 | 90.15 ± 15.74 | 1.17 |
| Owsley et al. (2007) | General vision | 57.2 ± 23.5 | 79.3 ± 15.8 | 1.10 |
| | Reading | 69.4 ± 27.5 | 93.6 ± 12.1 | 1.14 |
| | Ocular symptoms | 70.3 ± 29.8 | 86.3 ± 20.3 | 0.63 |
| | Mobility | 82.9 ± 18.2 | 93.5 ± 5.6 | 0.79 |
| | Psychological distress | 62.0 ± 27.0 | 77.7 ± 15.1 | 0.72 |
| | Activities of daily living | 92.5 ± 15.8 | 97.1 ± 9.3 | 0.35 |
| | Activities and hobbies | 85.2 ± 20.6 | 95.9 ± 11.9 | 0.64 |
| | Adaptation and coping | 83.8 ± 26.9 | 93.3 ± 14.6 | 0.44 |
| | Social interaction | 86.4 ± 20.1 | 98.1 ± 5.8 | 0.79 |
| Mamidipudi et al. (2003) | Self-care | 83.0 ± 4.3 | 83.3 ± 0.00 | 0.07 |
| | Mobility | 91.5 ± 13.5 | 98.2 ± 8.6 | 0.81 |
| | Social | 92.9 ± 17.9 | 98.8 ± 7.0 | 0.58 |
| | Mental | 73.7 ± 15.1 | 94.4 ± 4.7 | 0.66 |
| Fletcher et al. (1998) | Self-care | 53.35 ± 31.32 | 28.49 ± 34.20 | 0.92 |
| | Mobility | 36.15 ± 29.44 | 34.23 ± 34.91 | 1.18 |
| | Social | 35.01 ± 36.93 | 36.39 ± 43.88 | 0.98 |
| | Mental | 46.62 ± 32.97 | 27.83 ± 38.57 | 0.85 |
| Liu et al. (2004) | Self-care | 74.21 ± 18.05 | 98.15 ± 7.86 | 1.72 |
| | Mobility | 53.76 ± 25.40 | 95.68 ± 10.87 | 2.15 |
| | Social | 37.58 ± 34.87 | 84.26 ± 28.28 | 1.47 |
| | Mental | 66.29 ± 22.28 | 91.98 ± 18.20 | 1.26 |
| | Overall | 57.96 ± 21.30 | 92.52 ± 14.43 | 1.90 |

Effect size estimates are also provided

in countries with limited health-care resources. Considerably less improvement in patients' QoL is reported using generic instruments (Bilbao et al. 2009; Browne et al. 2008; Damiano et al. 1995; Pager et al. 2004; Rosen et al. 2005; Steinberg et al. 1994b; Marx et al. 1995; Gray et al. 2006; Mangione et al. 1994; Chandrasekaran et al. 2008; Pesudovs et al. 2003; Jayamanne et al. 1999). This is unsurprising since generic PROs contain little vision-related content and are therefore less sensitive to cataract-induced vision changes.

Cataract surgery also appears to improve VF in patients with other ocular conditions, such as age-related macular degeneration, diabetic retinopathy and glaucoma, particularly if the conditions have not progressed to the severe stages (Mozaffarieh et al. 2004, 2005, 2009; Lundstrom et al. 2002; El Mallah et al. 2001; Musch et al. 2006; Armbrecht et al. 2000, 2003). For example, using the IVI scale, cataract surgery significantly improves overall VSQoL in patients with early age-related macular degeneration compared to a delayed non-intervention group with the average gain in QoL being almost two-fold at follow-up in the early surgery group (Lamoureux et al. 2007b). Moreover, in the delayed surgery group, there was a large systematic deterioration of QoL suggesting that cataract surgery in AMD patients should be performed early before AMD has caused significant loss of acuity.

The QoL impact of 1st eye compared to 2nd eye cataract extraction is less clear (Table 10.3). Overall, it seems that 2nd eye surgery may afford VF and VSQoL benefits over and

**Table 10.3** Summary of studies using first generation instruments evaluating the impact of 1st and 2nd eye cataract extraction, and different treatment options on visual functioning (VF), vision-specific QoL (VSQoL) and generic health-related QoL HRQoL

| Outcome | VF | VSQoL | Generic HRQoL |
|---|---|---|---|
| 1st eye vs. 2nd eye | | | |
| Improvements after both 1st eye and 2nd eye surgery, greater after 1st eye | VF-14 (Gray et al. 2006; Castells et al. 1999)<br>ADVS (Elliott et al. 1997, 2000)<br>CSS (Gray et al. 2006) | | SIP (Castells et al. 1999)<br>GHQ (Gray et al. 2006) |
| Improvements after both 1st eye and 2nd eye surgery, greater after 2nd eye | VF-14 (Desai et al. 1996; Mozaffarieh et al. 2009; Castells et al. 2006)<br>CSS (Castells et al. 2006)<br>Catquest (Lundstrom et al. 1998, 2001) | VR-SIP (Desai et al. 1996) | SRS (Elliott et al. 2000)<br>SF-12 (mental domain) (Castells et al. 2006)<br>SIP (Desai et al. 1996) |
| Bilateral surgery on the same day has greater benefits than 1 eye at a time/expedited 2nd eye surgery has better QoL outcomes than routine 2nd eye surgery | Catquest (Lundstrom et al. 2006) | Laidlaw's (Laidlaw et al. 1998) | |
| Bilateral surgery had greater benefits over unilateral cataract surgery when the fellow eye had a significant cataract or poor presenting visual acuity | VF-9 (Lamoureux et al. 2009) | | |
| Treatment scenarios | | | |
| Both inpatient and outpatient groups improve PROs | VF-14 (Castells et al. 2001)<br>CSS (Castells et al. 2001) | | SIP (Castells et al. 2001) |
| 'Crucial' or 'appropriate' cataract surgery rating improves PROs more than 'uncertain or inappropriate' rating | VF-14 (Choi and Park 2009) | | |
| IOL types: | | | |
| Improvements with both monocular and multifocal IOLs but more improvement with multifocal IOLs | VF-14 (Cillino et al. 2008)<br>TyPE (Javitt and Steinert 2000; Tanaka et al. 2000; Berdeaux et al. 2008; Javitt et al. 1997, 2000; Lehmann et al. 2006) | | |
| Similar improvements with bilateral multifocal IOLs and conventional monofocal IOL pseudophakic monovision | | NEI-VFQ (Zhang et al. 2011) | |
| Largest improvements with full diffractive IOL compared to with apodised multifocal and monofocal IOLs | | NEI-VFQ (Alio et al. 2011) | |

(continued)

**Table 10.3** (continued)

| Outcome | VF | VSQoL | Generic HRQoL |
|---|---|---|---|
| Similar improvement after ReZoom, Tecnis and ReSTOR multifocal IOLs | VF-14 (Gierek-Ciaciura et al. 2009) | | |
| Similar improvement after aspherical IOLs and conventional spherical IOLs | ADVS (Denoyer et al. 2007) | NEI-VFQ (Amesbury et al. 2009) | |
| Improvement after both ICCE-AG and ECCE/PC-IOL lenses but significantly more with the latter | | Ellwein's (Fletcher et al. 1998; Oliver et al. 1998) | |
| Similar improvement with blue-light-filtering and non-blue-light-filtering IOLs | | NEI-VFQ (Espindle et al. 2005) | SF-12 (Espindle et al. 2005) |
| More improvements with phacoemulsification than extracapsular cataract extraction | VF-14 (Saw et al. 2002) | | |

*ADVS* Activities of Daily Vision Scale, *CSS* Cataract Symptom Scale, *ECCE/PC-IOL* Posterior Chamber IOL, *GHQ* General Health Questionnaire, *HRQoL* health-related quality of life, *ICCE-AG* intracapsular cataract extraction with aphakic glasses, *IOL* intraocular lens, *NEI-VFQ* National Eye Institute's Visual Function Questionnaire, *SIP* Sickness Impact Profile, *SRS* Self-Rating Scale, *VSQoL* vision-specific quality of life

above those gained by 1st eye surgery alone. Recent research comparing VF in patients undergoing surgery for either unilateral or bilateral cataract found that bilateral cataract surgery was associated with greater VF gains over unilateral cataract surgery *only when the fellow eye had a significant cataract or poor presenting visual acuity* (Tan et al. 2012). These findings support the current practice of second eye cataract surgery to be considered only when the fellow eye has significant cataract or reduced presenting visual acuity as second eye cataract surgery may not improve VF if the fellow eye has minimal cataract or good visual acuity. More research in these areas is warranted as this type of information may directly inform decisions about the application of cataract surgery in these patient groups.

Finally, but importantly, it appears that the use of modern psychometric methods to analyse PRO data can impact on the outcome of cataract surgery on QoL parameters. Two recent studies (Gothwal et al. 2010; Las Hayas et al. 2011) compared the use of traditional (summary scores) with modern psychometric methods (Rasch analysis) on the impact of cataract surgery on VF using different versions of the VF-14. While cataract surgery unequivocally improves VF, the Rasch-scaled versions of the VF-14 provided a more precise and objective measurement of the impact of cataract surgery on VF. Other studies using a Rasch-scaled version of the Catquest-9SF questionnaire have also reported significant improvement in VF following cataract surgery. (Lundstrom et al. 2009; Lundstrom and Pesudovs 2009)

## 10.3 Impact of Diabetic Retinopathy, Diabetic Macular Edema and Treatment Interventions on Quality of Life

### 10.3.1 Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes (Cheung and Wong 2009). Nearly all patients with type 1 diabetes and over 60 % of those with type 2 diabetes will develop some degree of DR after 20 years of

diabetes (Cheung et al. 2010). In its nonproliferative stages, DR is mostly asymptomatic but may cause significant and disabling vision loss once it progresses to severe nonproliferative DR (NPDR) and proliferative DR (PDR) stages. Furthermore, clinically significant diabetic macular edema (DME), which causes centralised vision loss, can occur at any stage (Wong and Klein 2008). The advanced stages of DR affect visual performance in a number of ways, including visual acuity, depth perception, colour and contrast sensitivity and visual field (Wong and Klein 2008) which, in turn, have considerable implications for patients' VF, VSQoL and emotional and social well-being (Fenwick et al. 2010, 2011a).

Optimal control of blood glucose, blood pressure and cholesterol are recognised as the most effective ways to prevent the development and progression of DR. Currently there are no pharmacologic drugs available to treat DR although research is currently being conducted on anti-VEGF peptides, retinal pigment epithelial cells and growth hormone inhibitors as potential areas for DR medications (Giuliari 2012). Once a patient has reached the vision-threatening (VTDR) stages of DR, photocoagulation laser treatment is usually performed to treat leaking blood vessels and prevent the onset of newly formed vessels in patients with PDR and to treat the areas affected by leaking vessels in patients with DME. It can be carried out over single or multiple sessions. Although laser treatment does not restore vision, it is highly effective in preventing further loss of visual acuity, especially if it is applied before significant central vision loss has occurred. If untreated, 26 % of eyes with PDR will progress to severe vision loss within 2 years; however, with laser treatment, this figure is reduced to 11 % (Watkins 2003). Although laser treatment remains the most effective way to treat VTDR, potential side effects such as loss of visual field, colour vision and contrast sensitivity can occur (Diabetes Control and Complications Trial Research Group 1995). If severe haemorrhaging or retinal detachment occurs, surgery becomes the only possible way to prevent further vision loss. Vitrectomy is the surgical procedure which is used to remove a vitreous haemorrhage or repair a detached retina. Prognosis for vision is good after vitrectomy, especially in instances of haemorrhage without retinal detachment (Porta and Bandello 2002).

It is now accepted that an assessment of the impact of DR on patients' QoL using a PRO measure is important for clinical trials, interventions or outcomes research to complement objective visual acuity information (Pesudovs et al. 2007). While there are a number of tools developed to measure the impact DR-related vision loss on QoL, to date, our understanding remains limited (Pesudovs 2006).

### 10.3.2 Impact of DR and DME on Health-Related Quality of Life

Generic health-related outcome measures such as the short-form (SF-12, -20 and -36) series (Ware and Sherbourne 1992; Ware et al. 1996; McHorney et al. 1993) are sometimes used to assess the impact of DR on health-related QoL (Table 10.4) (Lee et al. 1995; Hanninen et al. 1998) and findings generally indicate that DR and related vision impairment do have a negative impact. Significant reductions in physical and mental well-being due to DR, DME and visual acuity impairment have been reported, with a linear relationship evident between worsening visual acuity and declining health-related QoL scores (Davidov et al. 2009; Clarke et al. 2006). Severe vision loss or blindness tends to be a more important indicator of health-related QoL than severity level of DR, as patients with PDR under threat of vision loss have reported considerably better QoL than those with PDR and severe vision loss (Leksell et al. 2005).

In general, the use of generic health-related QoL instruments to explore condition-specific QoL is problematic because they measure perceived general health rather than VSQoL; that is, they have very little vision-related content (Bradley 2001). It is likely that any impact of vision impairment on generic health-related QoL will be lost in the noise of other non-vision-related impact on QoL in the overall score. This is important in DR research as the health-related

**Table 10.4** Summary of literature findings on the impact of DR on patient-reported outcome (PRO) instruments

| Study details | Patient characteristics | Patient-reported outcome measure | Aim of study[a] | Brief summary of findings |
|---|---|---|---|---|
| *Generic health-related QoL* | | | | |
| Clarke et al. (2006) | Type 2 diabetes, $n=?$ with DR | SF-36 | To obtain QoL measures and utility values associated with visual acuity in type 2 diabetics | All eight SF-36 domain scores were negatively associated with reduced visual acuity |
| Davidov et al. (2009) | Type 1 and type 2 diabetes, $n=207$ with DR | SF-12 | To describe the impact of co-morbidities, visual acuity, severity of DR and DME on QoL in people with diabetes | DR, DME and visual impairment have a considerable impact on the physical and mental components of generic HRQoL |
| Hanninen et al. (1998) | Type 2 diabetes (<65 years), $n=\sim33$ with DR | SF-20 | To compare the HRQoL in type 2 diabetic patients with age and gender-matched controls | The mean scores of all six SF-20 dimensions were 11–27 % lower in the type 2 diabetic patients than in the controls ($P<0.01$). DR did not impact on generic HRQoL, but reduced visual acuity did. Limited by very small number of participants with DR |
| Lee et al. (1995) | Diabetes type unspecified, $n=20$ with DR | SF-36 | To examine the relationship between VA and functioning and well-being in a diabetic sample | There was little or no correlation between VA or DR and generic HRQoL. Significant correlations were only found between physical functioning and role limitations caused by physical problems and worst eye VA. Severity of DR was not reported due to small number of participants with DR |
| Leksell et al. (2005) | Diabetes type unspecified, $n=44$ with DR | SWED-QUAL | To assess self-perceived health among people with diabetes who are blind or under threat of going blind compared to a reference group | Blind patients scored lower in 6 of the 13 health domains compared to the group under threat of blindness and the reference group. There were no differences in scores between patients under threat of becoming blind and the reference group. Thus, threat of blindness does not seem to affect generic HRQoL. Limited by small numbers of participants |
| *Utilities* | | | | |
| Brown et al. (1999) | Diabetes type unspecified, $n=100$ with DR | TTO and SG method | To calculate utility measures associated with vision loss from DR | Vision loss from DR is associated with a substantial increase in disutility and is directly dependent on the degree of visual loss |
| Brown et al. (2002) | Diabetes type unspecified, $n=333$ with DR | TTO method | To compare QoL in patients with vision loss from DR and AMD | Vision loss from both AMD and DR caused a similar increase in disutility |
| Huang et al. (2007) | Diabetes type unspecified, $n=19$ with DR | TTO method | To quantify utilities for an range of diabetes-related complications, including DR | DR utilities were equivalent to or worse than amputation utilities. Limited due to small number of patients with DR and only two levels of severity (presence of any DR, blindness) |

| | | | | |
|---|---|---|---|---|
| Lee et al. (2008) | Diabetes type unspecified, $n=116$ with DR | SG method | To compare utilities for five different eye diseases (including DR) using a perfect health and perfect vision scale | Utility levels decreased with worsening severity of DR. Utilities using the perfect vision scale were lower than using the perfect health scale, suggesting that the perfect vision scale may overestimate level of disutility |
| Lloyd et al. (2008) | Type 1 and type 2 diabetes, $n=122$ with DR and $n=47$ without DR | SG method, EQ-5D | To estimate disutility associated with different levels of DR severity using multiple methods | Declining levels of vision in diabetes is associated with substantial declines in utility using all utility methods. The decline in disutility is larger than reported in many other studies. Even relatively mild vision loss can be associated with substantial disutility |
| Shah et al. (2004) | Diabetes type unspecified, $n=88$ with DR | TTO method | To calculate utility measures associated with vision loss from DR and AMD | Vision loss from both AMD and DR caused a similar increase in disutility, although there was minimal difference between the mild and moderate groups |
| Sharma et al. (2002) | Diabetes type unspecified, $n=105$ with DR | TTO and SG method | To assess the validity of utilities in assessing QoL in patients with retinal disease (including DR, AMD and other retinal diseases) | Vision loss from retinal diseases is associated with a substantial increase in disutility and is directly dependent on the degree of visual loss. DR was not analysed directly |
| Sharma et al. (2003) | Diabetes type unspecified, $n=221$ with DR | TTO method | To compare utility results in a sample of Canadian and US patients with DR | Vision loss from DR in both the US and Canadian sample caused a similar increase in disutility |
| Smith et al. (2008) | Type 2 diabetes, $n=?$ with DR | EQ-5D | To estimate the impact of vision loss from diabetes using the EQ-5D | Declining levels of vision in diabetes ire associated with a reduction in utility. The decline in disutility was smaller than reported in other studies using the EQ-5D. Limited by small number of participants with vision impairment (levels below 6/12 rarely occurred) |
| Szabo et al. (2010) | Diabetes type unspecified, $n=98$ with DR | TTO method | To develop standardised descriptions of health states describing the impact of DR according to severity of VA and contrast sensitivity impairment in the better- and worse-seeing eye and to elicit preferences for these health states from persons with DR | Ten health states reflecting six clinically and patient-relevant combinations of better- and worse-seeing eye VA and contrast sensitivity were developed, based on items from the NEI-VFQ. Preferences decreased with increasing severity of functional impairment (i.e. worse VA, contrast sensitivity and bilateral disparity), independent of other sociodemographic and clinical characteristics. Mean preferences decreased from 0.98 (best health state) to 0.67 (worst health state) |
| Tung et al. (2005) | Type 2 diabetes, $n=86$ with DR and $n=286$ without DR | TTO method | To calculate utility measures associated with varying degrees of DR | Utility levels were generally higher than in other studies. Utility levels decreased with worsening severity of DR. Limited by small number of patients with severe levels of DR |

(continued)

**Table 10.4** (continued)

| Study details | Patient characteristics | Patient-reported outcome measure | Aim of study[a] | Brief summary of findings |
|---|---|---|---|---|
| *Visual functioning and QoL* | | | | |
| Ahmadian and Massof (2008) | Diabetes type not specified, $n=114$ with DR | AI (Massof 1995; Massof 1998) | To asses functional vision in patients with DR compared to age- and gender-matched controls with other eye pathologies | There was no statistically significant difference between patients with DR and control subjects in any of four functional domains. Therefore, visual impairment in patients with DR appears to be a generic and non-disease-specific outcome that can be explained mainly by the end impact of the disease in the patients' daily lives and not by the unique disease process that results in the visual impairment |
| Broman et al. (2002) | Diabetes type unspecified, $n=290$ with DR | NEI-VFQ-25 | To assess the impact of VA impairment and eye disease on VSQoL in a Hispanic population | Patients with DR had significantly lower scores in all subscales, many of which were not explained by level of VA |
| Cusick et al. (2005) | Type 1 and type 2 diabetes, $n=170$ with DR | NEI-VFQ-25 | | Worse central vision, as measured by VA, contrast sensitivity and visual fields, was associated with lower near and distance vision subscale scores in multivariate linear models |
| Gabrielian et al. (2010) | Type 1 and type 2 diabetes, $n=104$ with DR | NEI-VFQ-25 | To assess VSQoL in patients with NPDR and PDR | Patients with more severe levels of DR experience worse functioning and QoL than those with less severe levels, particularly on the role differences, near activities, distance activities, mental health and dependence subscales |
| Hariprasad et al. (2008) | Type 2 diabetes, $n=33$ with DME | NEI-VFQ-25 | To determine the impact of DME on QOL in patients with type 2 diabetes compared DR in type 1 diabetic patients and other eye pathology such as glaucoma, cataract and AMD | Scores for the DME group were significantly worse in general health and quality of vision than in the type 1 DR group. In addition, the DME group had lower mean scores in at least 10 of the 12 subscales than the glaucoma and cataract group, and in all scales compared to the reference (no DR) group. For the AMD group, only 3 were different. This suggests that functioning in DME patients is worse than most other eye pathologies but similar to that of AMD |
| Hirai et al. (2010) | Type 1 diabetes, $n=?$ with DR | NEI-VFQ-25 | To investigate changes in VSQoL during a 10-year period in a sample of people with type 1 diabetes | Change in visual acuity was the most important factor related to negative changes in all subscales. Loss of 3 lines was the most important factor relating to negative changes, and the most significant reductions were found in the general vision, mental health, role difficulties and driving subscales |

| | | | | |
|---|---|---|---|---|
| Klein et al. (2001) | Type 1 diabetes, $n=599$ with DR | NEI-VFQ-25 | To examine the association between VA and DR using the NEI-VFQ | In multivariate analyses, lower total scores were independently associated with poorer VA, more severe DR and presence of DME |
| Lamoureux et al. (2004b) | Diabetes type unspecified, $n=45$ with DR | IVI | To determine the restriction of participation in daily activities of people with DR | A poorer VA in the better eye correlated independently with poorer functioning and emotional well-being. The activities with the greatest functional decrease were reading print, mobility, work and leisure. The items of most concern to participants were worry about eyesight getting worse, frustration and feeling like a burden |
| Lamoureux et al. (2010b) | Diabetes type unspecified, $n=82$ with DR (Singapore Malay population) | VF-14 (modified version, VF-11) | To assess the impact of different levels of severity of DR on VF in an Asian population | When controlling for presenting VA, VTDR and PDR were the only levels of DR independently associated with poorer VF, and people with VTDR and PDR were 6–12 times more likely to report poorer functioning than those without these DR levels |
| Lloyd et al. (2008) | Type 1 and type 2 diabetes, $n=122$ with DR and $n=47$ without DR | NEI-VFQ-25 | To estimate disutility associated with different levels of DR severity using multiple methods | Diabetes-related vision loss, even at relatively mild levels, places substantial burden on functioning and QoL. NEI-VFQ-25 scores declined steadily with worsening VA |
| Loftus et al. (2011) | Diabetes type unspecified, $n=260$ with DME | NEI-VFQ-25 | To compare HR-VSQoL in patients with DME treated with intravitreous pegaptanib or sham injection in a RCT | Clinically meaningful improvements in the NEI-VFQ-25 domains near vision, distance vision and social functioning (week 54) and distance vision, social functioning, mental health and composite score (week 102) were reported in the group receiving pegaptanib compared to the sham group |
| Matza et al. (2008) | Type 1 and type 2 diabetes, $n=535$ with DR | NEI-VFQ-25 | To ascertain the degree of change in HRQoL associated with loss of VA among patients with DR | Change in VA was associated with corresponding changes in functioning and QoL. Compared to patients whose VA did not change, the group with >10 letters vision loss had significantly greater decreases in all but one subscale. Subscales with the greatest declines were dependency, driving, role limitations and mental health |
| Mazhar et al. (2010) | Type 2 diabetes, $n=486$ with DR | NEI-VFQ-25 and SF-12 | To assess the impact of DR and its severity on HRQoL among Latino patients | Greater severity of DR was associated with worse scores in all subscales of the NEI-VFQ and SF12. Those with mild NPDR through to unilateral moderate NPDR showed modest decline in QoL, whereas the decline became significantly steeper once disease progressed to bilateral NPDR through to bilateral PDR. The most significantly affected domains were daily activities, dependency and mental health |

(continued)

**Table 10.4** (continued)

| Study details | Patient characteristics | Patient-reported outcome measure | Aim of study[a] | Brief summary of findings |
|---|---|---|---|---|
| Mitchell et al. (2011) | Type 1 and type 2 diabetes, $n=345$ with DME | NEI-VFQ-25 | To compare clinical and VSQoL outcomes between ranibizumab monotherapy or combined with laser and laser alone over a 12-month study period in DME | Ranibizumab monotherapy or combined with laser provided superior visual acuity and VSQoL gains over standard laser in patients with visual impairment due to DME |
| Okamoto et al. (2008) | Diabetes type unspecified, $n=51$ with DR | NEI-VFQ-25 | To evaluate VSQoL and VF following vitrectomy for PDR | Severe vision impairment from PDR has a substantial negative impact on functioning and QoL which is ameliorated but not eliminated by vitrectomy |
| Tranos et al. (2004) | Diabetes type unspecified, $n=55$ with DR | NEI-VFQ-51 | To evaluate the effect of laser photocoagulation for DME on patients' VSQoL and to investigate associations between changes in self-reported VSQoL and changes in VA following application of laser treatment | There was a significant improvement in almost all aspects of functioning and QoL following laser photocoagulation treatment for DME, despite minimal improvements in VA |
| *Diabetic retinopathy-specific QoL* | | | | |
| Brose and Bradley (2009) | Type 1 and type 2 diabetes, $n=40$ with DR | RetDQoL | To assess the psychometric properties of the RetDQoL questionnaire | Greater vision impairment, worse DR and DME were associated with greater negative impact on QoL. In particular, participants with PDR reported significantly worse QoL than those with NPDR. DME was associated with significantly worse general and DR-specific QoL regardless of the severity of DR |
| Woodcock et al. (2004) | Type 1 and type 2 diabetes, $n=44$ with DR | RetDQoL | To develop a measure to assess the impact of DR on QoL using qualitative and quantitative methods | Qualitative data from semi-structured interviews with patients with DR and DME found that DR affected a number of facets of life such ADLs, mobility, leisure and emotional health, personal relationships, social life and diabetes management. The resulting questionnaire comprised 28 items designed to capture these issues |

Note: Studies are ordered alphabetically within each topic subsection

*Abbreviations* (alphabetical order): *ADL* activity of daily living, *AI* Activity Inventory, *AMD* age-related macular degeneration, *DME* diabetic macular edema, *DR* diabetic retinopathy, *HRQoL* health-related QoL, *IVI* Impact of Vision Impairment, *NEI-VFQ* National Eye Institute's Visual Function Questionnaire, *NPDR* nonproliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *QoL* quality of life, *RetDQoL* Retinopathy-Dependent QoL, *SF* short form, *SG* standard gamble, *SWED-QUAL* Swedish Health-Related Quality of Life Survey, *TTO* time trade-off, *VA* visual acuity, *VF* visual functioning, *VSQoL* vision-specific QoL, *VTDR* vision-threatening diabetic retinopathy

[a]Aims are as reported by the study authors

**Table 10.5** Utility values for DR severity using the TTO and SG

| Study | Overall | None[a] | Mild | Moderate | Severe | Blind |
|---|---|---|---|---|---|---|
| *Time trade-off* | | | | | | |
| Brown et al. (1999) | 0.77 | 0.85 | 0.78 | 0.78 | 0.64 | 0.59 |
| Brown et al. (2002)[b] | 0.79 | 0.86 | 0.80 | 0.77 | 0.60 | – |
| Sharma et al. (2002) | 0.77 | 0.91 | 0.80 | 0.71 | 0.62 | 0.47 |
| Sharma et al. (2003) | 0.79 | 0.88 | 0.79 | 0.73 | 0.73 | 0.49 |
| Shah et al. (2004)[c] | – | – | 0.88 | 0.90 | – | 0.76 |
| Huang et al. (2007)[d] | 0.53 | – | – | – | – | 0.38 |
| Tung et al. (2005)[e] | 0.92 | 0.94 | 0.87 | – | 0.83 | 0.81 |
| *Mean scores* | *0.76* | *0.89* | *0.82* | *0.78* | *0.68* | *0.58* |
| *Standard gamble* | | | | | | |
| Brown et al. (1999)[a] | 0.88 | 0.90 | 0.92 | 0.84 | 0.71 | 0.70 |
| Sharma et al. (2002)[a] | 0.85 | 0.95 | 0.90 | 0.77 | 0.74 | 0.60 |
| Lee et al. (2008)[f] | 0.77 | – | 0.91 | – | 0.60 | – |
| Lloyd et al. (2008)[g] | | 0.81 | 0.69 | 0.70 | 0.67 | 0.58 |
| *Mean scores* | *0.83* | *0.89* | *0.86* | *0.77* | *0.68* | *0.63* |

[a]Visual acuity in the better eye: none = 6/7.5 or better, mild = 6/9–6/15, moderate = 6/18–6/30, severe = 6/60–6/120, blind = CF-NLP
[b]Visual acuity in the better eye: none = 6/7.5 or better, mild = 6/9–6/12, moderate = 6/15–6/30, severe = ≤6/60
[c]Visual acuity in the better eye: mild = 6/6–6/12, moderate = 6/15–6/30, blind = ≤6/60
[d]Overall = symptomatic DR, blind = blindness
[e]None = no DR, mild = NPDR, severe = PDR, blind = blindness
[f]Mild = no or minimal background DR or clinically insignificant DME, moderate–severe = clinically significant DME, NPDR to PDR
[g]Visual acuity in the worse eye: none = 6/9 or better, mild = 6/12–6/18, moderate = 6/24–6/36, severe = 6/60–6/120, blind = CF-NLP

QoL decrements may be due to diabetes rather than DR *per se*.

### 10.3.3 Impact of DR/DME on Utilities

One common way of assessing health-related QoL for economic evaluation is through the estimation of utilities for the calculation of quality adjusted life years (QALYs) (Brazier et al. 2007). Utilities have typically been generated by using elicitation methods, such as the 'time trade-off (TTO)' and 'standard gamble (SG)' directly with patient cohorts. The scale of the utility index ranges between 0.0 and 1.0, where 0.0 represents death and 1.0 represents full health. States that are considered 'worse than death' are represented by negative utility values. By extension, the closer the utility value is to 0.0, the higher a person's disutility and vice versa (Brown et al. 1999).

TTO and SG methods have shown that utility tends to decrease steadily with worsening visual acuity resulting from DR (Table 10.5), although a considerable variance in overall scores is evident (Brown et al. 1999, 2002; Sharma et al. 2002, 2003; Shah et al. 2004; Huang et al. 2007; Tung et al. 2005; Lee et al. 2008; Lloyd et al. 2008). These discrepancies are concerning but may be related to differences in sample population particularly in terms of disease severity (visual impairment), sample size, study design and hypothetical scenarios used. There are also limitations associated with TTO and SG utility measures. For example, in TTO methodology, utility values can be influenced by duration effects and time preference effects, while in SG methodology, values may be contaminated by patients' attitudes to risk (Brazier et al. 2007). Moreover, a different scale is typically used in ophthalmology compared to other health states, namely, 'perfect vision' rather than 'perfect health'. It has been shown that patients with DR report higher disutility using the perfect vision scale when compared to the perfect health scale (Lee et al. 2008). This

means that studies using perfect vision as a scale may have overestimated the disutility associated with DR, as compared to other medical conditions where perfect health is used as a scale (Lee et al. 2008).

An alternative method for generating utilities is to use a multi-attribute utility instrument (MAUI) for measuring and valuing health-related QoL. In MAUIs, each life domain that may be affected by a health condition is assessed separately though a descriptive system including several health dimensions with associated levels of increasing severity (Brazier et al. 2007). A scoring algorithm, based upon general population values for health states defined by the descriptive system, is then applied to assign utilities to each health state described by the instrument. For MAUIs, the valuations are based on general population samples (usually country specific) while elicitation methods most often employ patient samples with the disease of interest. Generic MAUIs, including the EuroQol EQ-5D (Williams 1990), the Health Utilities Index (HUI-3) (Furlong et al. 2001), the 15D (Sintonen 2001), the SF-6D (Brazier and Roberts 2004) and the AQoL (Hawthorne et al. 1999), allow the comparison of utilities across a wide range of diseases and conditions because patients are able to rate their health status using a generic descriptive system.

However, assessment of the impact of DR and related vision impairment on health-related QoL using generic MAUIs has produced conflicting results. Small but significant decrements in utility values in patients with DR (Bagust and Beale 2005) or blindness caused by DR have been reported (Clarke et al. 2002). Others have shown a clear and systematic association between declining levels of visual acuity and reduced utility values (Lloyd et al. 2008; Smith et al. 2008). Many studies, however, have shown minimal, nonsignificant differences in EQ-5D utility values (Sakamaki et al. 2006; Glasziou et al. 2007; Kontodimopoulos et al. 2010), 15D utility values (Ahola et al. 2010) and SF-6D utility values for diabetic patients with and without DR/DME and pre- and post-anti-VEGF treatment for DME (Mitchell et al. 2011; Loftus et al. 2011). Indeed, in two recent studies by our group using the EQ-5D and the VisQoL (a vision-specific MAUI), we found no association between DR and DME, and utilities after adjusting for relevant clinical and sociodemographic covariates (Fenwick et al. 2011b; Fenwick et al. 2012). Only profound vision impairment was significantly associated with VisQoL utilities, but mild, moderate or severe vision impairment was not.

These differences may be due to the small sample sizes of many of these studies, especially at the severe spectrum of DR (Bagust and Beale 2005; Smith et al. 2008; Glasziou et al. 2007; Kontodimopoulos et al. 2010) or due to differences in study methodologies. Definitions of DR tend to range widely, from binary categorisations (e.g. 'proliferative DR' vs. 'blindness' (Bagust and Beale 2005) or presence of DR vs. absence of DR (Sakamaki et al. 2006)) to ordinal categorisations of visual acuity (Lloyd et al. 2008; Smith et al. 2008). Statistical analyses also vary between studies, including linear and ordinal regression models (Lloyd et al. 2008; Smith et al. 2008), tobit and censored least absolute derivations models (Clarke et al. 2002) and quantile regression models (Fenwick et al. 2011b), and this may have contributed to the equivocal findings. As the EQ-5D does not contain any vision-related content, it is also possible that it lacks sensitivity to evaluate the specific burden of DR-induced vision loss (Brenner et al. 1995). This hypothesis is supported by other studies using generic MAUIs that contain at least one item pertaining to vision, such as the HUI-3 and the 15D, which have shown significant declines in utilities due to DR and associated vision loss (Lloyd et al. 2008; Kontodimopoulos et al. 2010; Hahl et al. 2002).

While utilities provide a way for us to compare the impact of DR to other diseases, they are not optimal outcome measures. For those interested in outcomes, questionnaires that measure activity limitation or QoL are of greater interest because they provide a more holistic overview and focus on a range of areas such as physical disability, social health, psychological well-being and pain (Massof and Rubin 2001). They also provide health professionals like rehabilitation specialists greater precision and specificity in their measurements than utilities can afford (Massof and Rubin 2001).

### 10.3.4 Impact of DR and DME on Visual Functioning and Quality of Life

Despite heterogeneous study designs, study findings consistently indicate that DR impacts negatively on patients' VF and VSQoL, (Broman et al. 2002; Hariprasad et al. 2008) and that QoL worsens according to increased level of severity of DR (e.g. NPDR vs. PDR/VTDR) (Table 10.4) (Lamoureux et al. 2010a; Klein et al. 2001; Gabrielian et al. 2010). Vision impairment from DR also appears to have a negative, systematic relationship with VF and VSQoL, even in patients with mild/moderate vision loss (e.g. 6/12–6/18) (Lamoureux et al. 2004a; Lloyd et al. 2008; Cusick et al. 2005; Matza et al. 2008). However, the evidence with regard to VSQoL, as opposed to VF, is limited due to the restricted ability of the NEI-VFQ and IVI to provide a full assessment of QoL.

A DR-specific QoL tool (the Retinopathy-Dependent QoL or RetDQoL) (Woodcock et al. 2004) has recently been developed and validated (Brose and Bradley 2009) containing 26 items sampling various aspects of QoL including functional ability, social, family and working life, emotional well-being and self-care ability. It also contains two overview items, 'present QoL' and 'retinopathy-dependent QoL'. Studies using this instrument have reported that greater vision impairment, worse DR and DME are associated with a negative impact on QoL (Table 10.4). Specifically, participants with PDR reported significantly worse QoL than those with moderate or severe NPDR and, in turn, those with more severe stages of NPDR recorded significantly lower scores than those with mild NPDR. DME was associated with significantly worse general and DR-specific QoL regardless of the severity of DR. Importantly, the scores for the two overview items demonstrated worse DR-specific QoL than general QoL, suggesting that the presence of DR has a separate negative impact. This demonstrates the importance of not relying solely on generic measures when exploring a specific medical condition (Brose and Bradley 2009). Although more appropriate than a VSQoL or functioning tool, there are limitations associated with the development, validation and multiplicative scoring method of this instrument.

### 10.3.5 Impact of Treatment Interventions for DR and DME on Quality of Life

To date, the impact of treatment interventions on PROs is relatively unexplored (Table 10.4). Significant improvement in patients' VF and VSQoL following treatments for DR and DME, such as laser photocoagulation (Tranos et al. 2004) and vitrectomy surgery (Okamoto et al. 2008), have been reported even without significant corresponding improvements in visual acuity. However, VSQoL in patients following vitrectomy surgery remains lower than patients without VTDR, suggesting that VTDR still has a substantial QoL impact. Recently, several studies have reported significant VSQoL gains in patients with DR and DME following anti-VEGF treatment. For example, clinically meaningful improvements on several NEI-VFQ domains have been reported in patients with DME following intravitreal injections with pegaptanib sodium compared to a group receiving sham injections only (Loftus et al. 2011). Similarly, greater visual acuity and VSQoL gains have been demonstrated in patients receiving ranibizumab monotherapy or combined with laser, compared to laser therapy alone (Mitchell et al. 2011). Evidently, more research into patient-reported outcomes following both traditional and novel treatment interventions for DR and DME is required. With many clinical trials currently under way testing the efficacy of new treatment modalities for DR and DME, it is likely that this information will continue to emerge.

### 10.3.6 Current Limitations

Given the inherent differences between cataract, DR and DME, and associated treatment outcomes, it can be hypothesised that the QoL impact from

the two diseases also differs. For instance, cataract typically occurs only once in each eye, and it is reversible with cataract surgery which is usually highly successful. Cataract is generally accepted by patients as part of the ageing process and is not associated with another systemic disease. DR and DME, in contrast, are irreversible and available treatments such as laser therapy usually do not improve visual acuity, is often painful and may require several sessions. Similarly, patients are often fearful of having intraocular injections. Retinal bleeding may reoccur so patients must cope with the uncertainty of their eye condition. Treatment for DR such as vitrectomy increases patients' likelihood of developing other ocular conditions such as cataract and glaucoma. Moreover, unlike cataract, DR and DME do not affect everyone and patients may feel guilty due to poor diabetes control in the past. Therefore, it is likely that the impact on VF will be similar for the two conditions while the impact on patients' concerns, emotional well-being and inconvenience will be greater in those with DR and DME compared to cataract.

However, at present, comparing and contrasting the impact of both ocular conditions on all relevant QoL parameters is difficult due to inherent limitations in the PRO measures currently available. For instance, the content of most QoL instruments is suboptimal, focusing largely on vision-related activity limitation and containing only a small number of items assessing other relevant QoL issues such as emotional well-being, social relationships, concerns and convenience. Moreover, there are limitations associated with the development and validation of most available PROs. The most common one has been the use of Likert scoring to generate an assessment of the impact of DR and the use of Classical Test Theory validation techniques (Massof 2004). Additionally, since questionnaires must attempt to capture information relevant to people across the spectrum of disease severity using relatively few items, many instruments have failed to optimally target the respondents' level of VSQoL.

A rigorously developed and comprehensive QoL tool to measure the impact of ocular conditions and vision impairment on QoL is therefore lacking. Possible solutions include item banking and computer adaptive testing (CAT). An item bank is simply a pool of items that have been calibrated on the same scale using modern psychometric methods, such as Rasch analysis. An item bank measures a defined latent trait such as QoL, and the items in the item bank represent differing amounts of that latent trait along a continuum. (Cella et al. 2007) A working item bank enables the use of CAT which is a method for administering tests that adapts the questions asked to the examinee's ability level. CAT chooses and presents targeted items from a calibrated item bank to the respondent. Subsequent items are then selected based on the examinee's responses to previous questions, and selection proceeds until a predefined stopping criterion is reached (Gershon 2005).

### 10.3.7 Future Trends

A VF item bank measuring activity levels and goals in people with vision impairment has recently been developed (Massof et al. 2007). This work could be extended through the development of a multidimensional VSQoL item bank, which would be an important contribution to outcomes research in ophthalmology. Indeed, our group is currently developing and validating the Eye-tem bank to assess the impact of eye disease on QoL. The Eye-tem bank will be comprehensive, covering numerous ocular conditions, including diabetic retinopathy, glaucoma, age-related macular degeneration, cataract, and refractive error and amblyopia, among others. Items will assess multiple domains of QoL including visual symptoms, ocular surface symptoms, general symptoms, activity limitation, mobility, emotional, social, concerns, convenience and economic. The final Eye-tem bank will be applicable to clinical trials or intervention studies requiring accurate assessment of patient-reported outcomes, to clinicians in clinic settings, and to rehabilitation specialists assessing the needs of patients.

## Conclusions

The impact of cataract, DR and DME, and associated vision impairment on VF and QoL is clearly substantial, particularly at the severe spectrum of these conditions or when the disease is bilateral. Cataract surgery unequivocally improves VF and several aspects of VSQoL with large effect size values recorded in most studies. There is compelling evidence to demonstrate that cataract-surgery-induced vision gains are associated with severalfold improvements in critical daily living tasks such as reading newspapers or books; driving; watching TV; cooking; negotiating steps; sewing, knitting, crocheting or doing handicrafts; noticing traffic, information or shop signs; and recognising people. Although research using VSQoL instruments is limited, the evidence indisputably indicates that cataract surgery improves several VSQoL aspects. In addition to typical areas of functioning, cataract surgery improves several psychosocial aspects including social interaction, mental and emotional well-being, psychological distress, adaptation and coping. Research into the impact of treatment interventions for DR and DME, such as laser photocoagulation, vitrectomy and anti-VEGF injections on patients' VF and QoL, is limited to date, although improvements have been reported. More research into PROs associated with novel treatment interventions for DR, such as anti-VEGF and steroids, is required.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable

## References

Ahmadian L, Massof R (2008) Does functional vision behave differently in low-vision patients with diabetic retinopathy?–a case-matched study. Invest Ophthalmol Vis Sci 49:4051–4057

Ahola AJ, Saraheimo M, Forsblom C et al (2010) Health-related quality of life in patients with type 1 diabetes-association with diabetic complications (the FinDiane Study). Nephrol Dial Transplant 25:1903–1908

Alio JL, Plaza-Puche AB, Pinero DP et al (2011) Quality of life evaluation after implantation of 2 multifocal intraocular lens models and a monofocal model. J Cataract Refract Surg 37:638–648

Allen D (2008) Cataract. Clin Evid (Online) 2008:708–721

Alonso J, Espallargues M, Andersen TF et al (1997) International applicability of the VF-14. An index of visual function in patients with cataracts. Ophthalmology 104:799–807

Amesbury EC, Grossberg AL, Hong DM, Miller KM (2009) Functional visual outcomes of cataract surgery in patients with 20/20 or better preoperative visual acuity. J Cataract Refract Surg 35:1505–1508

Armbrecht AM, Findlay C, Kaushal S et al (2000) Is cataract surgery justified in patients with age related macular degeneration? A visual function and quality of life assessment. Br J Ophthalmol 84:1343–1348

Armbrecht AM, Findlay C, Aspinall PA, Hill AR, Dhillon B (2003) Cataract surgery in patients with age-related macular degeneration: one-year outcomes. J Cataract Refract Surg 29:686–693

Bagust A, Beale S (2005) Modelling EuroQol health-related utility values for diabetic complications from-CODE-2 data. Health Econ 14:217–230

Bassett K, Noertjojo K, Nirmalan P, Courtright P, Anderson D (2005) RESIO revisited: visual function assessment and cataract surgery in British Columbia. Can J Ophthalmol 40:27–33

Berdeaux G, Viala M, Roborel de Climens A, Arnould B (2008) Patient-reported benefit of ReSTOR multifocal intraocular lenses after cataract surgery: results of principal component analysis on clinical trial data. Health Qual Life Outcomes 6:10

Bilbao A, Quintana JM, Escobar A et al (2009) Responsiveness and clinically important differences for the VF-14 index, SF-36, and visual acuity in patients undergoing cataract surgery. Ophthalmology 116:418–24.e1

Bradley C (2001) Importance of differentiating health status from quality of life. Lancet 357:7–8

Brazier JE, Roberts J (2004) The estimation of a preference-based measure of health from the SF-12. Med Care 42:851–859

Brazier J, Ratcliffe J, Salomon J, Tsuchiya A (2007) Measuring and valuing health benefits for economic evaluation. Oxford University Press, Oxford

Brenner M, Curbow B, Legro MW (1995) THe proximal-distal continuum of multiple health outcomes measures: the case of cataract surgery. Med Care 33:AS236–AS244

Broman AT, Munoz B, Rodriguez J et al (2002) The impact of visual impairment and eye disease on vision-related quality of life in a Mexican-American population: proyecto VER. Invest Ophthalmol Vis Sci 43:3393–3398

Brose L, Bradley C (2009) Psychometric development of the individualized Retinopathy-Dependent Quality of Life Questionnaire (RetDQoL). Value Health 14:740–754

Brown MM, Brown GC, Sharma S, Shah G (1999) Utility values and diabetic retinopathy. Am J Ophthalmol 128:324–330

Brown MM, Brown GC, Sharma S, Landy J, Bakal J (2002) Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. Arch Ophthalmol 120:481–484

Browne J, Jamieson L, Lewsey J et al (2008) Case-mix & patients' reports of outcome in Independent Sector Treatment Centres: comparison with NHS providers. BMC Health Serv Res 8:78

Cassard SD, Patrick DL, Damiano AM et al (1995) Reproducibility and responsiveness of the VF-14. An index of functional impairment in patients with cataracts. Arch Ophthalmol 113:1508–1513

Castells X, Alonso J, Ribo C et al (1999) Comparison of the results of first and second cataract eye surgery. Ophthalmology 106:676–682

Castells X, Alonso J, Castilla M et al (2001) Outcomes and costs of outpatient and inpatient cataract surgery: a randomised clinical trial. J Clin Epidemiol 54:23–29

Castells X, Comas M, Alonso J et al (2006) In a randomized controlled trial, cataract surgery in both eyes increased benefits compared to surgery in one eye only. J Clin Epidemiol 59:201–207

Cella D, Gershon R, Lai JS, Choi S (2007) The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. Qual Life Res 16(Suppl 1):133–141

Chandrasekaran S, Wang JJ, Rochtchina E, Mitchell P (2008) Change in health-related quality of life after cataract surgery in a population-based sample. Eye (Lond) 22:479–484

Chang-Godinich A, Ou RJ, Koch DD (1999) Functional improvement after phacoemulsification cataract surgery. J Cataract Refract Surg 25:1226–1231

Cheung N, Wong T (2009) Diabetic retinopathy and systemic complications. In: Duh E (ed) Diabetic retinopathy. Humana Press, Totowa, pp 465–482

Cheung N, Mitchell P, Wong T (2010) Diabetic retinopathy. Lancet 376:124–136

Chew M, Chiang P, Zheng Y et al (2012) The impact of cataract, cataract types and grades on vision-specific functioning using Rasch analysis. Am J Ophthalmol 154:29–38.e2

Chia E, Wang J, Rochtchina E et al (2004) Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 45:71–76

Choi YJ, Park E-C (2009) Analysis of rating appropriateness and patient outcomes in cataract surgery. Yonsei Med J 50:368–374

Cillino S, Casuccio A, Di Pace F et al (2008) One-year outcomes with new-generation multifocal intraocular lenses. Ophthalmology 115:1508–1516

Clarke P, Gray A, Holman R (2002) Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 22:340–349

Clarke PM, Simon J, Cull CA, Holman RR (2006) Assessing the impact of visual acuity on quality of life in individuals with type 2 diabetes using the short form-36. Diabetes Care 29:1506–1511

Crabtree HL, Hildreth AJ, O'Connell JE et al (1999) Measuring visual symptoms in British cataract patients: the cataract symptom scale. Br J Ophthalmol 83:519–523

Cusick M, SanGiovanni JP, Chew EY et al (2005) Central visual function and the NEI-VFQ-25 near and distance activities subscale scores in people with type 1 and 2 diabetes. Am J Ophthalmol 139:1042–1050

Damiano AM, Steinberg EP, Cassard SD et al (1995) Comparison of generic versus disease-specific measures of functional impairment in patients with cataract. Med Care 33:AS120–AS130

Davidov E, Breitscheidel L, Clouth J, Reips M, Happich M (2009) Diabetic retinopathy and health-related quality of life. Graefes Arch Clin Exp Ophthalmol 247:267–272

Denoyer A, Le Lez M-L, Majzoub S, Pisella P-J (2007) Quality of vision after cataract surgery after Tecnis Z9000 intraocular lens implantation: effect of contrast sensitivity and wavefront aberration improvements on the quality of daily vision. J Cataract Refract Surg 33:210–216

Desai P, Reidy A, Minassian DC, Vafidis G, Bolger J (1996) Gains from cataract surgery: visual function and quality of life. Br J Ophthalmol 80:868–873

Diabetes Control and Complications Trial Research Group (1995) Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 102:647–661

Donovan JL, Brookes ST, Laidlaw DAH et al (2003) The development and validation of a questionnaire to assess visual symptoms/dysfunction and impact on quality of life in cataract patients: the Visual Symptoms and Quality of life (VSQ) Questionnaire. Ophthalmic Epidemiol 10:49–65

El Mallah MK, Hart PM, McClure M et al (2001) Improvements in measures of vision and self-reported visual function after cataract extraction in patients with late-stage age-related maculopathy. Optom Vis Sci 78:683–688

Elliott DB, Patla A, Bullimore MA (1997) Improvements in clinical and functional vision and perceived visual disability after first and second eye cataract surgery. Br J Ophthalmol 81:889–895

Elliott DB, Patla AE, Furniss M, Adkin A (2000) Improvements in clinical and functional vision and quality of life after second eye cataract surgery. Optom Vis Sci 77:13–24

Espallargues M, Alonso J (1998) Effectiveness of cataract surgery in Barcelona, Spain site results of an international study. Barcelona I-PORT investigators. International Patient Outcomes Research Team. J Clin Epidemiol 51:843–852

Espindle D, Crawford B, Maxwell A et al (2005) Quality-of-life improvements in cataract patients with bilateral

blue light-filtering intraocular lenses: clinical trial. J Cataract Refract Surg 31:1952–1959
Fenwick E, Pesudovs K, Rees G et al (2010) The impact of diabetic retinopathy: understanding the patient's perspective. Br J Ophthalmol 95:774–782
Fenwick E, Rees G, Pesudovs K et al (2011a) Social and emotional impact of diabetic retinopathy: a review. Clin Experiment Ophthalmol 40:27–38
Fenwick E, Xie J, Ratcliffe R et al (2011b) The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in Type 1 and Type 2 diabetes. Invest Ophthalmol Vis Sci 53:677–684
Fenwick E, Xie J, Pesudovs K et al (2012) Assessing disutility associated with diabetic retinopathy, diabetic macular edema and associated vision impairment using the VisQoL. Clin Exp Optom 95:362–370
Fletcher AE, Ellwein LB, Selvaraj S et al (1997) Measurements of vision function and quality of life in patients with cataracts in southern India. Report of instrument development. Arch Ophthalmol 115:767–774
Fletcher A, Vijaykumar V, Selvaraj S, Thulasiraj RD, Ellwein LB (1998) The Madurai Intraocular Lens Study. III: visual functioning and quality of life outcomes. Am J Ophthalmol 125:26–35
Friedman DS, Tielsch JM, Vitale S et al (2002) VF-14 item specific responses in patients undergoing first eye cataract surgery: can the length of the VF-14 be reduced? Br J Ophthalmol 86:885–891
Furlong WJ, Feeny DH, Torrance GW, Barr RD (2001) The Health Utilities Index (HUI (R)) system for assessing health-related quality of life in clinical studies. Ann Med 33:375–384
Gabrielian A, Hariprasad S, Jager R, Green J, Mieler W (2010) The utility of visual function questionnaire in the assessment of the impact of diabetic retinopathy on vision-related quality of life. Eye 24:29–35
Gershon RC (2005) Computer adaptive testing. J Appl Meas 6:109–127
Gierek-Ciaciura S, Cwalina L, Bednarski L, Mrukwa-Kominek E (2009) A comparative clinical study of the visual results between three types of multifocal lenses. Graefes Arch Clin Exp Ophthalmol 248:133–140
Giuliari GP (2012) Diabetic retinopathy: current and new treatment options. Curr Diabetes Rev 8:32–41
Glasziou P, Alexander J, Beller E, Clarke P, ADVANCE Collaborative Group (2007) Which health-related quality of life score? A comparison of alternative utility measures in patients with type 2 diabetes in the ADVANCE trial. Health Qual Life Outcomes 5:21
Gothwal VK, Wright TA, Lamoureux EL, Pesudovs K (2010) Measuring outcomes of cataract surgery using the Visual Function Index-14. J Cataract Refract Surg 36:1181–1188
Gray CS, Karimova G, Hildreth AJ et al (2006) Recovery of visual and functional disability following cataract surgery in older people: Sunderland Cataract Study. J Cataract Refract Surg 32:60–66
Hahl J, Hamalainen H, Sintonen H et al (2002) Health-related quality of life in type 1 diabetes without or with symptoms of long-term complications. Qual Life Res 11:427–436
Hanninen J, Takala J, Keinanen-Kiukaanniemi S (1998) Quality of life in NIDDM patients assessed with the SF-20 questionnaire. Diabetes Res Clin Pract 42:17–27
Hariprasad SM, Mieler WF, Grassi M et al (2008) Vision-related quality of life in patients with diabetic macular edema. Br J Ophthalmol 92:89–92
Hawthorne G, Richardson J, Osborne R (1999) The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. Qual Life Res 8:209–224
He MG, Xu JJ, Li SZ et al (1999) Visual acuity and quality of life in patients with cataract in Doumen County, China. Ophthalmology 106:1609–1615
Hirai FE, Tielsch JM, Klein BE, Klein R (2010) Ten-year change in vision-related quality of life in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Ophthalmology 118:353–358
Huang ES, Brown SFS, Ewigman BG, Foley EC, Meltzer DO (2007) Patient perceptions of quality of life with diabetes-related complications and treatments. Diabetes Care 30:2478–2483
Javitt JC, Steinert RF (2000) Cataract extraction with multifocal intraocular lens implantation: a multinational clinical trial evaluating clinical, functional, and quality-of-life outcomes. Ophthalmology 107:2040–2048
Javitt JC, Wang F, Trentacost DJ, Rowe M, Tarantino N (1997) Outcomes of cataract extraction with multifocal intraocular lens implantation: functional status and quality of life. Ophthalmology 104:589–599
Javitt J, Brauweiler HP, Jacobi KW et al (2000) Cataract extraction with multifocal intraocular lens implantation: clinical, functional, and quality-of-life outcomes. Multicenter clinical trial in Germany and Austria. J Cataract Refract Surg 26:1356–1366
Javitt JC, Jacobson G, Schiffman RM (2003) Validity and reliability of the Cataract TyPE Spec: an instrument for measuring outcomes of cataract extraction. Am J Ophthalmol 136:285–290
Jayamanne DGR, Allen ED, Wood CM, Currie S (1999) Correlation between early, measurable improvement in quality of life and speed of visual rehabilitation after phacoemulsification. J Cataract Refract Surg 25: 1135–1139
Kaplan RM, Tally S, Hays RD et al (2010) Five preference-based indexes in cataract and heart failure patients were not equally responsive to change. J Clin Epidemiol 64:497–506
Klein B, Klein R, Lee K, Cruickshanks K (1998) Performance-based and self-assessed measures of visual function as related to history of falls, hip fractures, and measured gait time. The Beaver Dam Eye Study. Ophthalmology 105:160–164
Klein R, Moss SE, Klein BEK, Gutierrez P, Mangione CM (2001) The NEI-VFQ-25 in people with long-term type 1 diabetes mellitus - the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Ophthalmol 119:733–740

Kontodimopoulos N, Pappa E, Chadjiapostolou Z et al (2010) Comparing the sensitivity of EQ-5D, SF-6D and 15D utilities to the specific effect of diabetic complications. Eur J Health Econ 13:111–120

Laidlaw DA, Harrad RA, Hopper CD et al (1998) Randomised trial of effectiveness of second eye cataract surgery. Lancet 352:925–929

Lamoureux E, Hassell J, Keeffe J (2004a) The determinants of participation in activities of daily living in people with impaired vision. Am J Ophthalmol 137:265–270

Lamoureux EL, Hassell JB, Keeffe JE (2004b) The impact of diabetic retinopathy on participation in daily living. Arch Ophthalmol 122:84–88

Lamoureux EL, Pallant JF, Pesudovs K et al (2007a) The impact of vision impairment questionnaire: an assessment of its domain structure using confirmatory factor analysis and Rasch analysis. Invest Ophthalmol Vis Sci 48:1001–1006

Lamoureux EL, Hooper CY, Lim L et al (2007b) Impact of cataract surgery on quality of life in patients with early age-related macular degeneration. Optom Vis Sci 84:683–688

Lamoureux E, Pesudovs K, Thumboo J, Saw S, Wong T (2009) An evaluation of the reliability and validity of the visual functioning questionnaire (VF-11) using Rasch analysis in an Asian population. Invest Ophthalmol Vis Sci 50:2607–2613

Lamoureux EL, Shyong Tai E, Thumboo J et al (2010) Impact of diabetic retinopathy on vision-specific function. Ophthalmology 117:757–765

Lamoureux EL, Fenwick E, Pesudovs K, Tan D (2011) The impact of cataract surgery on quality of life. Curr Opin Ophthalmol 22:19–27

Lansingh VC, Carter MJ, Martens M (2007) Global cost-effectiveness of cataract surgery. Ophthalmology 114: 1670–1678

Las Hayas C, Bilbao A, Quintana JM, Garcia S, Lafuente I (2011) A comparison of standard scoring versus Rasch scoring of the visual function index-14 in patients with cataracts. Invest Ophthalmol Vis Sci 52:4800–4807

Lee PP, Whitcup SM, Hays RD, Spritzer K, Javitt J (1995) The relationship between visual-acuity and functioning and well-being among diabetics. Qual Life Res 4:319–323

Lee BS, Kymes SM, Nease RF et al (2008) The impact of anchor point on utilities for 5 common ophthalmic diseases. Ophthalmology 115:898–903

Lehmann R, Waycaster C, Hileman K (2006) A comparison of patient-reported outcomes from an reported apodized diffractive intraocular lens and a conventional monofocal intraocular lens. Curr Med Res Opin 22:2591–2602

Leksell JK, Sandberg GE, Wikblad KF (2005) Self-perceived health and self-care among diabetic subjects with defective vision – a comparison between subjects with threat of blindness and blind subjects. J Diabetes Complications 19:54–59

Liu J, Xu J, He M (2004) The changes of quality of life in the patients after phacoemulsification with intraocular lens implantation. Yan Ke Xue Bao 20:135–139

Lloyd A, Nafees B, Gavriel S et al (2008) Health utility values associated with diabetic retinopathy. Diabet Med 25:618–624

Loftus JV, Sultan MB, Pleil AM (2011) Changes in vision- and health-related quality of life in patients with diabetic macular edema treated with pegaptanib sodium or sham. Invest Ophthalmol Vis Sci 52:7498–7505

Lundqvist B, Monestam E (2006) Longitudinal changes in subjective and objective visual function 5 years after cataract surgery Prospective population-based study. J Cataract Refract Surg 32:1944–1950

Lundqvist B, Monestam E (2009) Ten-year longitudinal visual function and Nd: YAG laser capsulotomy rates in patients less than 65 years at cataract surgery. Am J Ophthalmol 149:238–44.e1

Lundstrom M, Pesudovs K (2009) Catquest-9SF patient outcomes questionnaire: nine-item short-form Rasch-scaled revision of the Catquest questionnaire. J Cataract Refract Surg 35:504–513

Lundstrom M, Wendel E (2005) Duration of self assessed benefit of cataract extraction: a long term study. Br J Ophthalmol 89:1017–1020

Lundstrom M, Stenevi U, Thorburn W, Roos P (1998) Catquest questionnaire for use in cataract surgery care: assessment of surgical outcomes. J Cataract Refract Surg 24:968–974

Lundstrom M, Stenevi U, Thorburn W (2000a) Cataract surgery in the very elderly. J Cataract Refract Surg 26:408–414

Lundstrom M, Brege KG, Floren I, Stenevi U, Thorburn W (2000b) Impaired visual function after cataract surgery assessed using the Catquest questionnaire. J Cataract Refract Surg 26:101–108

Lundstrom M, Stenevi U, Thorburn W (2001) Quality of life after first- and second-eye cataract surgery: five-year data collected by the Swedish National Cataract Register. J Cataract Refract Surg 27:1553–1559

Lundstrom M, Brege KG, Floren I et al (2002) Cataract surgery and quality of life in patients with age related macular degeneration. Br J Ophthalmol 86:1330–1335

Lundstrom M, Albrecht S, Nilsson M, Astrom B (2006) Benefit to patients of bilateral same-day cataract extraction: randomized clinical study. J Cataract Refract Surg 32:826–830

Lundstrom M, Behndig A, Kugelberg M et al (2009) The outcome of cataract surgery measured with the Catquest-9SF. Acta Ophthalmol 89:718–723

Mamidipudi PR, Vasavada AR, Merchant SV, Namboodiri V, Ravilla TD (2003) Quality-of-life and visual function assessment after phacoemulsification in an urban Indian population. J Cataract Refract Surg 29:1143–1151

Mangione CM, Phillips RS, Lawrence MG et al (1994) Improved visual function and attenuation of declines in health-related quality of life after cataract extraction. Arch Ophthalmol 112:1419–1425

Marx MS, Werner P, Billig N et al (1995) Outcomes of cataract surgery in nursing home residents. Psychosomatics 36:254–261

Massof RW (1995) A systems model for low-vision rehabilitation. 1. Basic concepts. Optom Vis Sci 72:725–736

Massof RW (1998) A systems model for low vision rehabilitation. II. Measurement of vision disabilities. Optom Vis Sci 75:349–373

Massof RW (2004) Likert and Guttman scaling of visual function rating scale questionnaires. Ophthalmic Epidemiol 11:381–399

Massof RW, Rubin GS (2001) Visual function assessment questionnaires. Surv Ophthalmol 45:531–548

Massof RW, Ahmadian L, Grover LL et al (2007) The Activity Inventory: an adaptive visual function questionnaire. Optom Vis Sci 84:763–774

Matza LS, Rousculp MD, Malley K, Boye KS, Oglesby A (2008) The longitudinal link between visual acuity and health-related quality of life in patients with diabetic retinopathy. Health Qual Life Outcomes 6:95

Mazhar K, Varma R, Choudhury F et al (2010) Severity of diabetic retinopathy and health-related quality of life the Los Angeles Latino Eye Study. Ophthalmology 116:1496–1504

McCarty C, Nanjan M, Taylor H (2001) Vision impairment predicts 5 year mortality. Br J Ophthalmol 85: 322–326

McGwin G Jr, Scilley K, Brown J, Owsley C (2003) Impact of cataract surgery on self-reported visual difficulties: comparison with a no-surgery reference group. J Cataract Refract Surg 29:941–948

McHorney CA, Ware JE Jr, Raczek AE (1993) The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31:247–263

Mitchell P, Bandello F, Schmidt-Erfurth U et al (2011) The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 118:615–625

Mozaffarieh M, Krepler K, Heinzl H, Sacu S, Wedrich A (2004) Visual function, quality of life and patient satisfaction after ophthalmic surgery: a comparative study. Ophthalmologica 218:26–30

Mozaffarieh M, Heinzl H, Sacu S, Wedrich A (2005) Clinical outcomes of phacoemulsification cataract surgery in diabetes patients: visual function (VF-14), visual acuity and patient satisfaction. Acta Ophthalmol Scand 83:176–183

Mozaffarieh M, Heinzl H, Sacu S, Wedrich A (2009) Second eye cataract surgery in the diabetes patient? Quality of life gains and speed of visual and functional rehabilitation. Ophthalmic Res 41:2–8

Musch DC, Gillespie BW, Niziol LM et al (2006) Cataract extraction in the collaborative initial glaucoma treatment study: incidence, risk factors, and the effect of cataract progression and extraction on clinical and quality-of-life outcomes. Arch Ophthalmol 124:1694–1700

Nanayakkara S (2009) Vision-related quality of life among elders with cataract in Sri Lanka: findings from a study in Gampaha District. Asia Pac J Public Health 21:303–311

Norregaard JC (2007) Results from the International Cataract Surgery Outcomes Study. Acta Ophthalmol Scand 85:5–32

Norregaard JC, Bernth-Petersen P, Alonso J, Andersen TF, Anderson GF (2003) Visual functional outcomes of cataract surgery in the United States, Canada, Denmark, and Spain: report of the International Cataract Surgery Outcomes Study. J Cataract Refract Surg 29:2135–2142

Okamoto F, Okamoto Y, Fukuda S, Hiraoka T, Oshika T (2008) Vision-related quality of life and visual function following vitrectomy for proliferative diabetic retinopathy. Am J Ophthalmol 145:1031–1036

Oliver JE, Thulasiraj RD, Rahmathullah R et al (1998) Vision-specific function and quality of life after cataract extraction in south India. J Cataract Refract Surg 24:222–229

Owsley C, McGwin G Jr, Scilley K et al (2007) Impact of cataract surgery on health-related quality of life in nursing home residents. Br J Ophthalmol 91: 1359–1363

Pager CK (2004) Assessment of visual satisfaction and function after cataract surgery. J Cataract Refract Surg 30:2510–2516

Pager CK, McCluskey PJ, Retsas C (2004) Cataract surgery in Australia: a profile of patient-centred outcomes. Clin Experiment Ophthalmol 32:388–392

Pesudovs K (2006) Patient-centred measurement in ophthalmology–a paradigm shift. BMC Ophthalmol 6:25

Pesudovs K, Weisinger HS, Coster DJ (2003) Cataract surgery and changes in quality of life measures. Clin Exp Optom 86:34–41

Pesudovs K, Burr JM, Harley C, Elliott DB (2007) The development, assessment, and selection of questionnaires. Optom Vis Sci 84:663–674

Pokharel GP, Selvaraj S, Ellwein LB (1998) Visual functioning and quality of life outcomes among cataract operated and unoperated blind populations in Nepal. Br J Ophthalmol 82:606–610

Polack S, Kuper H, Wadud Z, Fletcher A, Foster A (2008) Quality of life and visual impairment from cataract in Satkhira district, Bangladesh. Br J Ophthalmol 92: 1026–1030

Polack S, Eusebio C, Fletcher A, Foster A, Kuper H (2010) Visual impairment from cataract and health related quality of life: results from a case–control study in the Philippines. Ophthalmic Epidemiol 17:152–159

Porta M, Bandello F (2002) Diabetic retinopathy – a clinical update. Diabetologia 45:1617–1634

Prager TC, Chuang AZ, Slater CH, Glasser JH, Ruiz RS (2000) The Houston Vision Assessment Test (HVAT): an assessment of validity. The Cataract Outcome Study Group. Ophthalmic Epidemiol 7:87–102

Rao GN, Khanna R, Payal A (2011) The global burden of cataract. Curr Opin Ophthalmol 22:4–9

Resinkoff S, Passcolini D, Daniel E et al (2004) Global data on visual impairment in the year 2002. Bull World Health Organ 82:844–851

Rosen PN, Kaplan RM, David K (2005) Measuring outcomes of cataract surgery using the Quality of Well-Being Scale and VF-14 Visual Function Index. J Cataract Refract Surg 31:369–378

Sakamaki H, Ikeda S, Ikegami N et al (2006) Measurement of HRQL using EQ-5D in patients with type 2 diabetes mellitus in Japan. Value Health 9:47–53

Saw S-M, Tseng P, Chan W-K et al (2002) Visual function and outcomes after cataract surgery in a Singapore population. J Cataract Refract Surg 28:445–453

Shah VA, Gupta SK, Shah KV, Vinjamaram S, Chalam KV (2004) TTO utility scores measure quality of life in patients with visual morbidity due to diabetic retinopathy or ARMD. Ophthalmic Epidemiol 11:43–51

Sharma S, Brown GC, Brown MM et al (2002) Validity of the time trade-off and standard gamble methods of utility assessment in retinal patients. Br J Ophthalmol 86:493–496

Sharma S, Oliver-Fernandez A, Bakal J et al (2003) Utilities associated with diabetic retinopathy: results from a Canadian sample. Br J Ophthalmol 87: 259–261

Sintonen H (2001) The 15D instrument of health-related quality of life: properties and applications. Ann Med 33:328–336

Smith DH, Johnson ES, Russell A et al (2008) Lower visual acuity predicts worse utility values among patients with type 2 diabetes. Qual Life Res 17:1277–1284

Steinberg EP, Tielsch JM, Schein OD et al (1994a) The VF-14: an index of functional impairment in patients with cataract. Arch Ophthalmol 112:630–638

Steinberg EP, Tielsch JM, Schein OD et al (1994b) National study of cataract surgery outcomes. Variation in 4-month postoperative outcomes as reflected in multiple outcome measures. Ophthalmology 101:1131–1140; discussion 40–41

Superstein R, Boyaner D, Overbury O (1999) Functional complaints, visual acuity, spatial contrast sensitivity, and glare disability in preoperative and postoperative cataract patients. J Cataract Refract Surg 25:575–581

Szabo S, Beusterten K, Pleil A et al (2010) Patient preferences for diabetic retinopathy health states. Invest Ophthalmol Vis Sci 51:3387–3394

Tan A, Tay W, Zheng Y et al (2012) The impact of bilateral or unilateral cataract surgery on visual functioning: when does second eye cataract surgery benefit patients? Br J Ophthalmol 96:846–851

Tanaka T, Yamakawa N, Mizusawa T, Usui M (2000) Cataract extraction with multifocal intraocular lens implantation: clinical functional, and quality-of-life outcomes: multicenter clinical trial in Germany and Austria. J Cataract Refract Surg 26:1356–1366

Taylor AE, Shah SP, Gilbert CE et al (2008) Visual function and quality of life among visually impaired and cataract operated adults. The Pakistan National Blindness and Visual Impairment Survey. Ophthalmic Epidemiol 15:242–249

Tielsch JM, Steinberg EP, Cassard SD et al (1995) Preoperative functional expectations and postoperative outcomes among patients undergoing first eye cataract surgery. Arch Ophthalmol 113:1312–1318

Tranos PG, Topouzis F, Stangos NT et al (2004) Effect of laser photocoagulation treatment for diabetic macular edema on patient's vision-related quality of life. Curr Eye Res 29:41–49

Tung TH, Chen SJ, Lee FL et al (2005) A community-based study for the utility values associated with diabetic retinopathy among type 2 diabetics In Kinmen, Taiwan. Diabetes Res Clin Pract 68:265–273

Uusitalo RJ, Brans T, Pessi T, Tarkkanen A (1999) Evaluating cataract surgery gains by assessing patients' quality of life using the VF-7. J Cataract Refract Surg 25:989–994

Walker JG, Anstey KJ, Hennessy MP, Lord SR, von Sanden C (2006) The impact of cataract surgery on visual functioning, vision-related disability and psychological distress: a randomized controlled trial. Clin Experiment Ophthalmol 34:734–742

Wang J, Mitchell P, Cumming R, Smith W (2003) Visual impairment and nursing home placement in older Australians: the Blue Mountains Eye Study. Ophthalmic Epidemiol 10:3–13

Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483

Ware J Jr, Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34:220–233

Watkins PJ (2003) ABC of diabetes – retinopathy. Br Med J 326:924–926

WHOQOL Group (1997) Measuring quality of life. The World Health Organisation, Geneva, pp 1–13

Williams A (1990) EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 16:199–208

Wong T, Klein K (2008) The epidemiology of eye diseases in diabetes. In: Ekoé J, Rewers M, Williams R, Zimmet P (eds) The epidemiology of diabetes mellitus, 2nd edn. Wiley, Oxford, pp 475–497

Woodcock A, Bradley C, Plowright R et al (2004) The influence of diabetic retinopathy on quality of life interviews to guide the design of a condition-specific, individualised questionnaire: the RetDQoL. Patient Educ Couns 53:365–383

Yuen L, Do NH, Vu QL et al (2011) Cataract surgical outcomes, visual function and quality of life in four rural districts in Vietnam. Clin Experiment Ophthalmol 39:119–125

Zhang F, Sugar A, Jacobsen G, Collins M (2011) Visual function and spectacle independence after cataract surgery: bilateral diffractive multifocal intraocular lenses versus monovision pseudophakia. J Cataract Refract Surg 37:853–858

Zhao J, Sui R, Jia L, Fletcher AE, Ellwein LB (1998) Visual acuity and quality of life outcomes in patients with cataract in Shunyi County, China. Am J Ophthalmol 126: 515–523

# Glaucoma and Quality of Life

# 11

Suzanne W. van Landingham
and Pradeep Y. Ramulu

## Abbreviations

| | |
|---|---|
| AFREV | Assessment of Function Related to Vision |
| MD | Mean deviation |
| MVA | Motor vehicle accident |
| NEI VFQ | National Eye Institute Visual Functioning Questionnaire |
| VF | Visual field |

## 11.1 Importance of Studying Quality of Life in Glaucoma

Over 60 million people worldwide are affected by glaucoma, and disease prevalence is highest among the elderly (Quigley and Broman 2006). While effective treatments are available, there is no definitive cure, and many people continue to lose vision from this disease. Older people with glaucoma are at highest risk of experiencing disability due to more advanced visual field (VF) loss and other age-related factors (Mukesh et al. 2002; Leske et al. 2001). Understanding how glaucoma affects quality of life and disability has important ramifications for medical decision-making, developing rehabilitation programs, and allocating social services.

### 11.1.1 Measuring Quality of Life Is Important

Before discussing the impact of glaucoma on quality of life, it is important to define "quality of life." Quality of life describes a person's overall satisfaction with his/her life, a purely mental state. It is immensely important, as it reflects a person's overall well-being and ability to function in his/her environment, but can be difficult to assess. It may be measured in general terms, or indirectly, by assessing its components. Because it can be measured concretely and may be addressable by rehabilitation, disability is an important component of quality of life and will be addressed in this chapter.

The study of quality of life has broad medical and social applications. It is important for understanding the impact of disease and identifying those who need rehabilitation and/or a change in medical therapy. Disabilities identified as having a strong impact on quality of life can be targeted for rehabilitation. Quality of life can also be used as an outcome measure to assess the effectiveness of rehabilitation programs. Finally, an understanding of the impact of disease on quality of life is important when balancing independence and safety (e.g., when discussing driving cessation).

Quality of life can influence medical decision-making. If the stage of glaucoma at which individuals experience decreased quality of life is

S.W. van Landingham (✉)
P.Y. Ramulu, MD, MHS, PhD
Wilmer Eye Institute,
Johns Hopkins University School of Medicine,
600 North Wolfe St., Maumenee B-110,
Baltimore, MD 21287, USA
e-mail: swestbr3@jhmi.edu; pramulu1@jhmi.edu

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_11, 

identified, treatment can be optimized to maximize quality of life and minimize unnecessary interventions. Patients can also be educated about functional changes likely to occur in their lives with continued disease progression. Furthermore, quality of life measures can be used to assess the efficacy of therapies, particularly because they may reflect both the preservation of visual abilities and the potential side effects of therapy.

Finally, quality of life can impact medical policy-making. Payments for medical treatment and rehabilitation are authorized on the assumption that they improve patients' lives. As such, quality of life measures can be used to justify reimbursement for treatment or rehabilitation. Quality of life or disability measures can also justify FDA approval of new therapies by providing evidence of real-world impact.

### 11.1.2 How to Approach Patients in a Clinical Setting

Knowledge of how glaucoma and glaucoma treatment affect quality of life can help us approach patients in a clinical setting. It can help us assess the implications of the disease worsening: given the patient's current VF and rate of disease progression, is he/she likely to experience a decrease in quality of life? Does prospective disability outweigh the potential downsides of treatment? Consideration of these issues can facilitate the optimization of treatment plans.

Similarly, it is important to take into account the individual's subjective experience of the disease and its impact on their quality life when developing a treatment plan. What are the patient's priorities? What can they no longer do because of VF loss, and what abilities do they hope to maintain despite VF loss? Considering these questions facilitates empathy and strengthens the patient-doctor relationship.

Finally, understanding the impact of glaucoma on patients' quality of life can help identify individuals who require rehabilitation and facilitate referral to appropriate rehabilitation programs.

## 11.2 Spectrum of Disease

### 11.2.1 Disability in Glaucoma: When or If?

Glaucoma can cause bilateral blindness, and it is obvious that complete vision loss is disabling. Many individuals with glaucoma only experience mild to moderate vision loss, however, so it is important to determine the point in disease progression at which different activities are affected and to treat accordingly. Unlike other causes of age-related vision loss, such as cataract, glaucomatous damage is irreversible, so treatment must be proactive. As with any medical condition, however, treatment can have dangerous side effects. Determining the degree of vision loss that causes significant disability will help determine the point at which treatment should be more aggressive. Furthermore, functional parameters could potentially be used to tailor this decision to the individual patient.

Some previous studies using global measures of quality of life have shown no substantial correlation between VF loss and disability. The Collaborative Initial Glaucoma Treatment Study (CIGTS) showed only small-magnitude correlations between impairment of visual activities and better-eye VF loss in subjects with unilateral or early bilateral disease (Mills et al. 2001; Mills 1998). In several studies, less than 25 % of subjects with glaucoma were willing to trade any longevity for perfect vision, indicating that most glaucoma patients do not perceive their VF loss as a major disability (Aspinall et al. 2008; Jampel et al. 2002b).

Other studies, however, do link VF loss with substantial decrements in quality of life. In the Los Angeles Latino Eye Study (LALES), even mild (2–6 dB) unilateral VF loss was associated with lower quality of life scores (McKean-Cowdin et al. 2007). A study based at the Wills Eye Institute showed a significant correlation between binocular VF loss and the Assessment of Disability Related to Vision (ADREV) test (Richman et al. 2010). In the Proyecto Ver Eye Project, subjects with glaucoma had lower vision-related quality of life scores than subjects with cataract or diabetic retinopathy (Broman et al. 2002). Furthermore, the effect of glaucoma of

any stage was greater than that of two lines of visual acuity loss in nearly all functional domains studied (Broman et al. 2008).

More study is needed to clarify the stage of glaucomatous VF loss required to effect quality of life. Perhaps this issue is best approached by considering different functional domains separately, as this would adjust for potentially conflicting effects and could be more clinically relevant. It would also be helpful to specify precisely the level of disability in order to practically interpret these results. Further work is also necessary to determine to what extent the impact of all-cause VF loss (as might be measured in a population-based survey) reflects the impact of VF loss from glaucoma.

### 11.2.2 Staging Glaucoma to Predict Quality of Life

In discussions of glaucoma progression, it is important to describe disease severity in clinically relevant stages. For a staging system to be clinically relevant, it must help direct therapy and be readily measurable in clinic. This is challenging: the manifestation and progression of glaucoma vary greatly between individuals, and there are numerous possible measurement methodologies. Many staging systems exist, but none has been appropriately validated with disability. Here, we will examine some issues germane to glaucoma staging for quality of life purposes and discuss some previously developed systems.

An important initial decision in describing glaucoma progression is whether to use categorical variables, such as mild, moderate, or severe, or continuous variables, such as mean deviation (MD). Categorical variables are typically easier for patients, policy-makers, and other non-ophthalmologists to understand: imagine hearing "you have severe glaucoma" compared to hearing "you have a mean deviation of negative 22." It also makes it easy to separate patients into groups for interventions. Some granularity is lost in the use of categorical variables, however, and the division of individuals with a continuous symptom (vision loss) into discrete groups will always be somewhat arbitrary. Continuous variables more accurately describe disease, but are not as useful for communicating with patients. Cutoffs can be applied to continuous variables in order to separate patients into therapeutic groups.

Another issue is whether better eye, worse eye, or integrated VFs best predict function. Many investigators have related disability to MD of the better- or worse-functioning eye. This approach is useful because monocular MD is readily available to clinicians, but it does not take into account the real-world use of binocular vision or the impact of the field defect's location.

Other investigators have developed MD-based scores in clinical trials. This allows for the division of patients into sensible groups for descriptive and therapeutic purposes. Scales were developed for the Advanced Glaucoma Intervention Study (AGIS) (Anon 1994), Collaborative Initial Glaucoma Treatment Study (Musch et al. 1999), and by investigators at Bascom Palmer (Hodapp et al. 1993). Comparisons of these systems have been made in several reviews (Brusini and Johnson 2007; Mills et al. 2006; Susanna and Vessani 2009). Many of the systems were developed with the intention of creating a universal system to be used across different studies, though none has yet been broadly accepted.

Binocular VFs are a logical method for assessing the relationship of visual function and quality of life, as individuals use both eyes in the real world. The Esterman VF (Esterman 1982), in which VFs are measured binocularly, was promising but has been shown to be inferior to better-eye MD in predicting self-reported quality of life (Jampel et al. 2002a) and driving ability (Crabb et al. 2004). This may be partly due to the suprathreshold technology, which can misestimate vision loss. Several methods of posttest VF integration have been developed, as well (Crabb et al. 2004; Nelson-Quigg et al. 2000). These methods have the advantage of using information that is already collected in a standard clinic visit; the patient is not required to complete an additional test. In one analysis, however, combined VFs were highly correlated with and not more predictive than better-eye MD on ten functional measures (Unpublished data from the Salisbury Eye

Evaluation). So, combined VFs and better-eye MD are equally effective quality of life metrics.

A final issue to consider in analyzing visual function is whether to take into account the effect of VF damage in different loci. Several studies have broached this topic (van Gestel et al. 2010; Coleman 2007; Black et al. 2011), but they do not take into account the typical progression of glaucomatous damage through different areas of the VF. For example, subjects with inferior vision loss may perform worse than those with superior defects because inferior loss typically comes later in the course of the disease: their poor performance may not be due to defect location, rather, to the sum of their field loss. Further study that controls for the presence of VF defects in multiple locations is needed. Susanna and colleagues have addressed defect location in their new staging system, but it has yet to be validated with quality of life or disability measures (Susanna and Vessani 2009).

Overall, current evidence supports the use of better-eye MD, as it is reasonably well validated and is also clinically accessible. It is logical that integrated or binocular VFs would better predict real-world functioning, but perhaps an appropriate system has not yet been developed.

## 11.3 Assessing Changes in Quality of Life Due to Glaucoma

### 11.3.1 What Tasks and Functions Are Affected in Glaucoma?

Quality of life has many components, and it is important to determine which are most likely to be affected by glaucoma in order to better target studies and interventions. Several investigators have asked patients to self-report the elements of quality of life that they struggle with using focus groups and/or questionnaires.

In developing the National Eye Institute Visual Functioning Questionnaire (NEI VFQ), Mangione and colleagues used focus groups to determine what elements of quality of life are most difficult for those with a variety of eye diseases (Mangione et al. 1998). The 82 glaucoma participants reported the most problems with mobility (including driving) and reading. Specifically, 34 % cited difficulty driving at night, 32 % driving during the daytime, and 29 % reading ordinary print.

Several investigators have used questionnaires to address the same question. Forty percent of participants with glaucoma in the Collaborative Initial Glaucoma Treatment Study identified difficulty with bright light and with moving from light to dark (Janz et al. 2001). In another study, subjects with glaucoma were significantly more likely to report difficulty with mobility tasks (using stairs and bumping into things) and object finding (Viswanathan et al. 1999). A third study found that glaucoma subjects reported trouble seeing in the dark more often than normal-sighted controls (82 % of glaucoma subjects vs. 32 % of controls) (Lee et al. 1998). Yet another investigation surveyed 63 subjects and found that 70 % reported difficulty with glare, 54 % had difficulty adapting to different levels of light, 49 % had difficulty with steps, 42 % with shopping, and 36 % with crossing a road (Nelson et al. 1999).

Other investigators have used questionnaire data to rank potentially challenging tasks in order of difficulty (Burr et al. 2007; Bhargava et al. 2006; Aspinall et al. 2008). Burr ranked tasks of central and near vision as most difficult for glaucoma subjects, followed by mobility and other activities of daily living. Bhargava and colleagues ranked driving as the most difficult of several tasks. Finally, Aspinall and colleagues ranked reading, getting around outside the home, glare, object bumping, and then the performance of household chores as the most difficult tasks (in order of descending difficulty).

While slightly different sets of tasks were evaluated in each of these studies, several areas clearly emerged as particularly problematic for people with glaucoma: reading, mobility, and driving, with particular emphasis on the effect of lighting changes on these tasks. These areas should therefore be targeted for future study and rehabilitation efforts.

### 11.3.2 How to Measure Quality of Life

In order to study the effect of glaucoma on quality of life, it is important to choose the instrument best suited to the question at hand. Here, we will

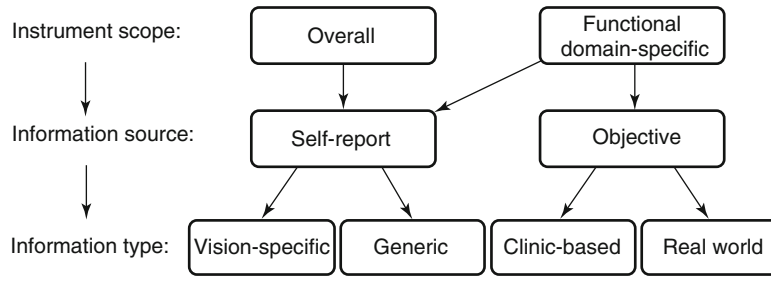


**Fig. 11.1** Study design issues for research concerning quality of life in glaucoma. This flow chart outlines some of the choices that must be considered in designing a study or selecting an instrument to measure quality of life in glaucoma

discuss several important decisions that must be made when choosing or designing an instrument (Fig. 11.1). Will it assess overall quality of life or functional domain-specific quality of life? Will it rely on self-report or objective measurements? If self-report, will it target vision-specific tasks or generic ones? If objective, will it be clinic-based or real world? The benefits of and problems with each approach will be discussed below.

An important initial choice concerns the scope of the study: will it assess overall quality of life or specific functional domains? Assessments of overall quality of life can take into account many different components of a person's life. They are especially useful for studies of cost-efficacy of an intervention, such as a comprehensive rehabilitation program. Such a broad scope can, however, lose some granularity. Functional domain-specific studies, on the other hand, allow investigators to identify important areas of disability in individuals with good global functioning and to draw more specific, actionable conclusions. This approach can, however, complicate public health conclusions and comparisons to non-ocular diseases.

Another important choice is the information source: will it be self-report or an objective measurement? Self-report is important because it takes into account the individual's experience of their disease, which defines quality of life. Self-report is prone to confounding, however, by factors such as depression, comorbid illness, and more. Reporting bias is also influential and is particularly important to consider when assessing domains for which individuals may be motivated to exaggerate or minimize a disability. Examples of reporting bias in domains relevant to the study of glaucoma and quality of life include poor agreement noted between self- and state-reported accident numbers in a study of older drivers (McGwin et al. 1998) and the inferiority of self-reported to objectively measured physical activity in predicting biomarkers (Atienza et al. 2011). Self-report may be further biased by the development of compensatory mechanisms that allow an individual to avoid the task in question. For instance, an individual who cannot drive because of low vision may not complain of difficulty with driving because they no longer drive.

Objective measurement has the obvious advantage of allowing the investigator to observe and measure a subject's disability firsthand. It is helpful in measuring the effect of rehabilitation tools. However, it cannot measure the individual's perceived functionality, which may be as important as technical ability to quality of life.

Within the category of self-report, an instrument may be generic or vision-specific. An example of a generic measure is the time trade-off ("How many years of your life would you trade to have perfect vision?") (Jampel et al. 2002b). Generic instruments are useful from a public health standpoint, as they allow comparison of the impact of vision loss to that of other diseases. They are also easily understandable by policymakers and investigators in other disciplines. They are particularly prone to confounding, however, as it can be difficult to distinguish the effects of glaucoma from comorbid conditions.

Vision-specific self-report instruments are more useful than generic ones for assessing the effect of a visual intervention or the changes in quality of life within the context of disease progression. Compared to generic self-report instruments, they have less need for an external standard to establish the significance of changes and are less prone to bias by confounding variables, but they make comparisons of glaucoma

with non-ocular diseases difficult. Examples of vision-specific self-report instruments include the NEI VFQ-25 (Mangione et al. 2001) and the Activities of Daily Vision Scale, which was used in the Salisbury Eye Evaluation (SEE) (Mangione et al. 1992).

Objective measurements cannot directly measure quality of life, but can quantify aspects of disability which are very pertinent to function, independence, and well-being. They may be clinic-based or real world. Most previously used objective measures of quality of life have assessed performance in the clinic. One such instrument is the five-item "Assessment of Function Related to Vision" (AFREV), which correlated well with the NEI VFQ-25 and measures of visual ability (Altangerel et al. 2006). It gave rise to a similar metric called the "Assessment of Disability Related to Vision," a nine-task instrument designed to capture a broader range of disability (Lorenzana et al. 2009). Both measures have been used in additional studies (Skalicky and Goldberg 2008; Richman et al. 2010) and were originally validated by Rasch analysis, though subsequent papers reported results on a Likert scale without weighting tasks of varying difficulty.

Clinic-based objective measures have the advantage of allowing direct observation and standardization of the patient task for easy comparison. They are also potentially applicable in the low-vision clinic setting to identify specific deficits or areas for rehabilitation. Dougherty and colleagues recently developed and used a battery of functional tests for low vision in a pilot study to assess the success of low-vision rehabilitation (Dougherty et al. 2009). Few other investigators have yet used an objective measure for this purpose.

The Salisbury Eye Evaluation found a substantial correlation between performance on tasks performed at home and in clinic (West et al. 1997b). So, clinic-based assessments are a reasonable approximation of real-world performance for activities that can be reproduced in clinic, such as reading, dialing a telephone, climbing stairs, and reaching for objects.

Certain key activities, however, such as driving and overall physical activity, cannot be adequately reproduced in a clinical setting. Ramulu and colleagues have assessed mobility in glaucoma subjects in the real-world setting by outfitting subjects with an accelerometer and a cellular tracking device for wear during a normal week of activity (Ramulu et al. 2011; Ramulu et al. 2012a, b). Real-world driving ability was assessed as part of the Salisbury Eye Evaluation (West et al. 2010), though the population was not enriched for or specifically evaluated for glaucoma, making conclusions about the effect of glaucoma on real-world driving ability difficult (West et al. 1997a). Real-world quality of life assessment remains a promising growth area in glaucoma research.

Overall, in assessing the effect of glaucoma on quality of life, there are a number of choices to consider. Decisions about instrument scope, information source, and information type may all vary depending on the goal of the study and the resources available to the investigator.

## 11.4 Specific Elements of Quality of Life Affected by Glaucoma

In this section, we will discuss the impact of glaucoma on specific elements of quality of life that have been identified as problem areas for glaucoma patients. We will focus on components that can be objectively measured and that are potential targets for rehabilitation, including mobility (driving, physical activity, and walking), balance, falls, and reading.

### 11.4.1 Driving

The ability to drive is important for quality of life and independent living for many older adults. In the United States and other developed countries, most adults rely on driving as their primary mode of transportation (Eberhard 1998). Furthermore, as discussed earlier, retaining the ability to travel outside the home is a high priority for people with glaucoma. For these reasons, establishing the impact of glaucoma on driving is an important objective of glaucoma and quality of life research.

Previous studies have established that glaucoma affects driving, though the nature of that effect and the stage of the disease at which it occurs are still disputed. Many studies have shown people with glaucoma to be at higher risk for driving cessation (Gilhotra et al. 2001; Ramulu et al. 2009a; van Landingham et al. 2013). Drivers with glaucoma also report greater difficulty with driving, and perceived difficulty increases with severity of VF loss (Freeman et al. 2008; Gutierrez et al. 1997; Parrish et al. 1997). Studies have differed on whether drivers with glaucoma are more likely to limit their driving. The Salisbury Eye Evaluation found no significant associations between glaucoma and driving limitations in an older (mean age 79.5) rural cohort (Ramulu et al. 2009a). Three other studies conducted in younger individuals driving in more urban settings demonstrated more frequent driving limitations among people with glaucoma (McGwin et al. 2004; Adler et al. 2005) and greater limitations with increasing disease severity (van Landingham et al. 2013). When people with glaucoma do limit their driving, they tend to limit driving in low visibility conditions (such as at night), in unfamiliar areas, and in heavy traffic.

The impact of limitation and cessation of driving in glaucoma on driver safety is unclear. It is possible that those who limit their driving succeed in reducing their risk of motor vehicle accident (MVA) to a level similar to or lower than that of normal-sighted drivers. This hypothesis is supported by work showing that having glaucoma actually decreases older individuals' risk of MVA (McGwin et al. 2004; Hu et al. 1998). A second possibility is that individuals with glaucoma who have limited their driving still drive poorly and/or unsafely. This idea is supported by studies showing that VF loss is a risk factor for MVAs (Johnson and Keltner 1983; Rubin et al. 2007; McGwin et al. 2005). Other studies have shown that drivers with glaucoma make more driving errors in driving simulations (Coeckelbergh et al. 2002; Szlyk et al. 2002) and direct on-road evaluations of driving (Keay et al. 2009) and that these errors increase with VF loss (Szlyk et al. 2005). Further study is needed to determine the ideal amount and setting of driving for people with glaucoma in order to balance the competing priorities of safety and independence.

Knowing that people with glaucoma may limit or cease their driving, we must consider how this change impacts their quality of life. Driving cessation has been associated with incident depression and increased risk of entry into a long-term care facility, even after controlling for demographic and health variables (Ragland et al. 2005; Marottoli et al. 1997; Freeman et al. 2006). One study, however, found that higher-risk (low visual attention score) drivers who self-regulated their driving did not experience reduced social engagement (Okonkwo et al. 2008). This topic merits further consideration.

There are several methodological options for studying driving in people with glaucoma, including questionnaires/self-report, simulation, and real-world observation. Questionnaire data is good for assessing attitudes toward driving and, to some extent, voluntary limitations, but may not accurately reflect driving records (McGwin et al. 1998). Individuals may try to conceal driving limitations or poor driving behaviors out of fear of being reported to licensing authorities. Some researchers have obtained objective crash data from state agencies (Johnson and Keltner 1983), which prevents self-report bias but may result in underestimation of MVA rates anyway, as minor MVAs ("fender benders") are often resolved without involvement of the police.

Driving simulator (Coeckelbergh et al. 2002; Szlyk et al. 2002) and fixed-course road tests have been used to evaluate driving skills and are similar to the on-road driving tests used in license renewal procedures for older drivers. Driving simulation studies have even been proposed as a way to predict global visual functioning in glaucoma (Medeiros et al. 2011). They do not, however, capture the full variety of driving scenarios that is experienced in real life. Also, these exams typically require subjects to drive in an unfamiliar "car," incompletely recreate the visual and auditory inputs involved in driving, omit the vestibular input employed while driving, and cannot reflect voluntary limitations of driving.

A meaningful way to study driving in people with glaucoma would be to observe the driver unobtrusively in the real-world setting. The Salisbury Eye Evaluation Driving Study (SEEDS) and other studies have used in-car cameras to observe older adults' driving habits, though not specifically glaucoma subjects (Lee et al. 2003; West et al. 2010). This methodology would be particularly effective at capturing poor driving habits that may occur frequently, such as running red lights or unsafe lane changes. MVAs may be more difficult to study, as they are rare events and are therefore less likely to be captured during a study period.

Thus far, we have discussed driving ability for glaucoma patients as a group. We will briefly consider how driving ability should be regulated for persons with glaucoma on the individual level, as well, for purposes of patient counseling and licensing. Given our current level of knowledge, patients with glaucoma should be considered at risk for unsafe driving, but because of the potential impact of driving cessation on quality of life, physicians should proceed with caution when recommending driving cessation. At the same time, physicians have a responsibility for the safety of their patients and, in some states, could be held liable for accidents caused by vision-impaired patients whom they have not referred to licensing authorities (Anon 2011).

No evidence has supported absolute VF cutoffs for determining driving status, and some studies have suggested that measures of visual ability other than traditional perimetry are a better suited to predicting MVAs in older drivers (Emerson et al. 2011; Ball et al. 1993). One such measure is the useful field of view (UFOV), which takes into account visual attention and the ability to compensate for reduced VF with head movements (Clay et al. 2005). Currently, most states recommend that physicians refer to the authorities for an on-road driving test any patient whose vision puts them at risk for poor driving (Anon 2010). Individuals with advanced unilateral or bilateral VF loss may be at higher risk for poor driving, and physicians should discuss driving habits with these individuals and consider referring them for evaluation by certified driving instructors if their vision or cognitive ability is felt to put them and others at risk.

### 11.4.2 Activity and Walking

Walking and physical activity are important to maintaining health and quality of life in old age, and both may be affected by glaucomatous vision loss. Individuals performing less physical activity have a higher risk of mortality (Kaplan et al. 1987) and are more likely to have or acquire numerous undesirable conditions, including cardiovascular disease (Bijnen et al. 1998), osteoporosis (Cummings et al. 1985), and obesity (Yu et al. 2007). Furthermore, more physical activity has been associated with better subjective well-being (Lynch et al. 2008; Garatachea et al. 2009). Because of the importance of physical activity and the fact that difficulty walking is a common complaint in glaucoma (Nelson et al. 1999; Viswanathan et al. 1999), the relationship between glaucoma and walking/physical activity merits consideration.

Several investigations have shown poor mobility performance in glaucoma and all-cause VF loss. In the Salisbury Eye Evaluation, all-cause VF loss was associated with slower walking speed and more bumping into objects (Patel et al. 2006; Friedman et al. 2007). Kuyk and colleagues similarly showed a correlation between VF loss and orientation errors, bumping into objects, and decreased walking speed in low-vision subjects (Kuyk et al. 1998). Turano and colleagues also showed slower walking speeds in glaucoma subjects, with mobility performance worse with worsening VF (Turano et al. 1999).

Other studies have demonstrated reduced physical activity and walking in glaucoma and VF loss. Ramulu and colleagues used accelerometers to demonstrate that physical activity is lower at greater levels of glaucomatous VF damage (Ramulu et al. 2012a, b). They did not find group differences in physical activity when comparing glaucoma and glaucoma suspects with normal vision, but this may be due to limited sample size rather than true absence of difference. Moreover, subjects with advanced glaucoma (better-eye

mean deviation of −13 dB or worse) had statistically significant, severe restrictions in physical activity, engaging in only one-third as much moderate to vigorous physical activity as normal controls. Similarly, in the nationally representative sample of the National Health and Nutrition Examination Survey (NHANES), subjects with bilateral any-cause VF loss took 17 % fewer steps per day and engaged in 30 % less accelerometer-measured moderate/vigorous physical activity than subjects with normal VFs after accounting for numerous demographic and health variables (van Landingham et al. 2012).

Walking and mobility are common complaints in glaucoma, and there is substantial evidence supporting an impact of glaucoma and VF loss on physical activity. However, most low-vision programs in the USA lack a walking and/or mobility program (Owsley et al. 2009). Further study is merited about the most effective way to prevent deconditioning in people with vision loss and to rehabilitate those who are already less active. Walking and mobility programs should also be made more available to the many vision-impaired people who could benefit from them.

### 11.4.3 Falls and Balance

Falls and balance are two related areas of particular concern for personal safety in glaucoma. Falls are the leading cause of injury-related death in the elderly (Anon 2006) and are increased in glaucoma (Haymes et al. 2007; Lamoureux et al. 2008; Black et al. 2011). Colón-Emeric and colleagues also used Medicare data to demonstrate glaucoma to be a risk factor for entry into a skilled nursing facility with hip fracture in men but not women (Colón-Emeric et al. 2003). Several studies show increased risk of falls in VF loss of any cause (Freeman et al. 2007). In the Beaver Dam Eye Study, VF loss doubled participants' risk of both falls and hip fractures (Klein et al. 1998). Coleman estimated that one-third of all falls in a cohort of elderly women were caused by severe binocular VF loss (Coleman 2007). Finally, a study of Medicare beneficiaries with glaucoma showed that those with VF loss were significantly more likely to fall and to have had a femur fracture than those without VF loss (Bramley et al. 2008). Dhital and colleagues have reviewed falls and vision loss (Dhital et al. 2010).

Impaired balance is a likely mechanism of falls in glaucoma. Several studies have found an association between glaucomatous VF loss and a decrease in balance (Shabana et al. 2005; Black et al. 2008; Friedman et al. 2007). Greater postural sway has also been observed in subjects with glaucoma compared to controls. This difference disappears when subjects closed their eyes, indicating that the difference is in fact due to loss of visual input and not due to confounding variables (Shabana et al. 2005; Black et al. 2008).

Given the effect of glaucoma on falling and balance, it is logical that glaucoma leads to fear of falling (Ramulu et al. 2012a, b). Fear of falling in turn may contribute to the decreased walking described above and to social isolation, both of which could directly impact quality of life.

Many lines of evidence suggest that older adults with glaucoma are at increased risk for falls, including injurious falls. The interrelationships of glaucomatous VF loss, balance, falls, fear of falling, and walking are complex (Fig. 11.2). More attention to fall-related rehabilitation in glaucoma patients is merited to avoid this preventable cause of injury and death.

### 11.4.4 Reading

Reading is an important element of quality of life. Traditionally, glaucoma has not been thought to affect reading until late in the disease: many believe that reading is affected by loss of visual acuity and not by the scotomas and peripheral vision loss of mild to moderate glaucoma. People with glaucoma complain about difficulty reading throughout the course of the disease, however (Nelson et al. 1999; Burr et al. 2007; Broman et al. 2002). In terms of specific complaints, glaucoma patients also reported difficulty following a line and finding the next line of print while reading (Viswanathan et al. 1999).

Difficulties with reading have been observed in several clinic-based trials. Reading small print

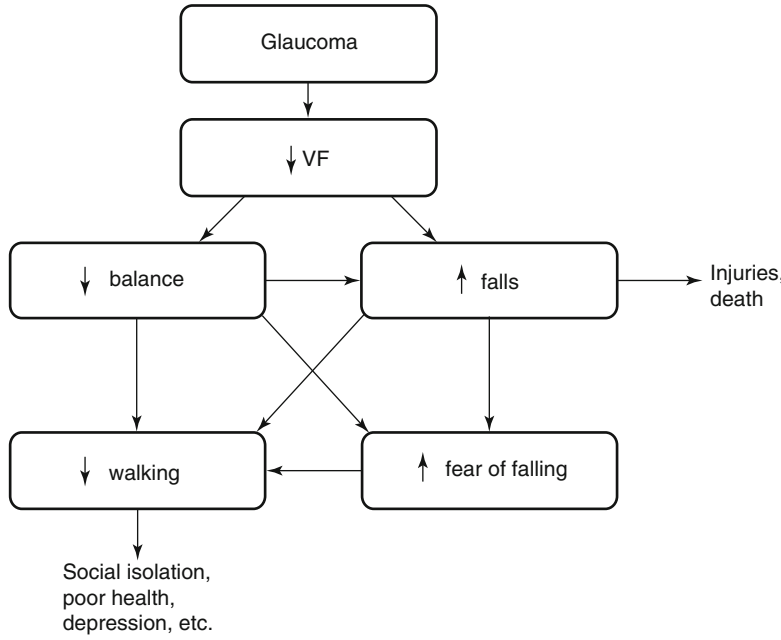


**Fig. 11.2** Effect of glaucomatous VF loss on balance, falls, fear of falling, and walking. This flow chart outlines some of the complex interrelationships of VF loss, balance, falls, fear of falling, and walking in glaucoma

was identified as one of the most visually difficult tasks for individuals with glaucoma during development of the AFREV, with a difficulty level similar to finding small objects (Altangerel et al. 2006). In the Salisbury Eye Evaluation, severe bilateral glaucoma was associated with slower reading speed when reading for short durations (Ramulu et al. 2009b). In another investigation, 12 % of glaucoma subjects could not read the print on standard medicated eye drop bottles, highlighting the potential health hazards of reading impairment (O'Hare et al. 2009).

There seems to be a disconnect between the problems with reading identified by patients and the deficits noted on objective testing. The two studies discussed above seem to support the traditional belief that reading is affected in glaucoma only by the visual acuity loss occurring late in the disease: one study reports reduced reading speed only in severe, bilateral glaucoma, and the other reports difficulty in reading small print. Note that the AFREV evaluation assessed only reading small print and reading in dim illumination, which are likely to be affected by reduced contrast sensitivity and visual acuity, and not items that are more likely to be affected by mild to moderate glaucomatous VF loss, such as finding words on a page or reading speed. The Salisbury Eye Evaluation tested only out loud reading speed, which may be affected differently from silent reading, in a population not enriched for people with glaucoma. Even so, it showed a nonsignificant increase in the odds of reading impairment for subjects with unilateral glaucoma.

Future investigations of the impact of glaucoma on reading should include patients with mild to moderate glaucoma in order to determine what type of glaucomatous vision loss affects reading and at what stage of the disease reading is substantially affected. They should also examine different components of reading, including reading speed, scanning for specific words, reading small text, sustained silent book reading, and computer reading.

### 11.4.5 Prehension

One domain where glaucoma patients have shown impairment is in prehension, measured with "reaching and grasping" tasks (Kotecha et al. 2009). This may be caused by poor spatial awareness (Fortenbaugh et al. 2007) leading to poor

visual search performance (Smith et al. 2011). Prehension is necessary for many elements of life, including feeding oneself, cleaning, work-related tasks, and cooking. Impaired prehension could make all of these basic activities difficult and less efficient.

### 11.4.6 Glare/Adjusting to Lighting Changes

Complaints of glare and problems adapting to lighting changes are very common in those with glaucoma and can be correlated with the extent of VF loss (Lee et al. 1998; Nelson et al. 1999; Burr et al. 2007). Objectively measured difficulty with glare and dark adaptation has also been associated with glaucomatous VF loss (Nelson et al. 2003; Janz et al. 2009). In fact, Nelson and colleagues found that difficulty with glare and dark adaptation was more strongly associated with VF loss and perceived disability than was difficulty with tasks of central, near, or peripheral vision for glaucoma subjects.

Glare and difficulty adjusting to lighting changes can affect a person's ability to drive. In a clinic-based study using self-report outcomes, more than 50 % of drivers with glaucoma reported having at least "some" difficulty with glare-related driving tasks, including "trouble driving with headlights from oncoming cars in my field of view" and "at night in the rain, trouble seeing the road because of headlights from oncoming cars" (Janz et al. 2009). These glare-related driving problems are more common than complaints about driving tasks requiring peripheral vision ("difficulty changing lanes in traffic because of trouble seeing cars in the next lane") and visual search ("when driving at night, objects from the side unexpectedly appear in my field of view"). They also rank as more difficult in Rasch analysis, which is surprising considering the attention given to VF loss in studies of disability in glaucoma.

Difficulty with glare and adjusting to lighting changes has also been shown to affect glaucoma patients' ability to see at night, walk in the dark, and find dropped objects (Nelson et al. 2003). These abilities are important to performing activities of daily living. Impairment in these abilities can also represent a safety hazard: if a person with glaucoma has difficulty seeing in the dark, he/she may be at higher risk for injurious falls.

### 11.4.7 Institutionalization

It is well established that there is a higher prevalence of glaucoma among nursing home populations than in the noninstitutionalized elderly (Eichenbaum et al. 1999). A study of Medicare records showed that the presence of glaucomatous vision loss of any Medicare-defined severity level puts individuals at increased risk of institutionalization (Bramley et al. 2008).

The mechanism underlying the association of glaucoma with institutionalization is unclear. Glaucoma could cause institutionalization directly by causing severe vision loss. A person who is unable to see well enough to perform activities of daily living may require nursing home care, especially in the absence of family support or low-vision services. Glaucoma may also impact nursing home admissions through an intermediary. For instance, glaucoma may lead to injurious falls, leading to disability or fear of falling and the perceived inability to live independently. Glaucomatous vision loss may lead to depression, which can also influence the need for nursing home care.

Alternatively, the relationship of glaucoma with institutionalization may be confounded by other disabling illnesses. Alzheimer's dementia, for instance, is associated with glaucoma (Duthie et al. 2011) and with nursing home admissions (Banaszak-Holl et al. 2004). Some patients may be admitted primarily due to their dementia but have comorbid glaucoma.

Several factors probably contribute to the association between glaucoma and institutionalization. Regardless of the precise mechanism, it can be viewed as an embodiment of the profound effect glaucoma can have on quality of life and disability. Nursing home admission can have a large impact on quality of life and can be very expensive to the individual and/or the

health-care system. Clarification of the mechanism relating glaucoma to institutionalization could lead to strategies for patient rehabilitation and the prevention of excessive nursing home admissions.

## Conclusions

The relationship between glaucoma and quality of life is immensely important. As discussed above, glaucoma can affect a person's overall perception of disability and quality of life. It can also affect many related functional domains, including mobility, falls, balance, reading, and more. Further study of how glaucoma affects quality of life could lead to more informed medical decision-making, improved ability to counsel patients, and more effective rehabilitation strategies.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Adler G et al (2005) Driving habits and patterns in older men with glaucoma. Soc Work Health Care 40(3): 75–87

Altangerel U, Spaeth GL, Steinmann WC (2006) Assessment of function related to vision (AFREV). Ophthalmic Epidemiol 13(1):67–80

Anon (1994) Advanced Glaucoma Intervention Study. 2. Visual field test scoring and reliability. Ophthalmology 101(8):1445–1455

Anon (2006) Fatalities and injuries from falls among older adults – United States, 1993–2003 and 2001–2005. MMWR Morb Mortal Wkly Rep 55(45):1221–1224

Anon (2010) Physician's guide to assessing and counseling older drivers, 2nd edn. American Medical Association, Chicago. Available at: http://www.ama-assn.org/ama/pub/physician-resources/public-health/promoting-healthy-lifestyles/geriatric-health/older-driver-safety/assessing-counseling-older-drivers.page? Accessed 13 Jan 2012

Anon (2011) Medical reporting fact sheet. Available at: http://www.dmv.state.pa.us/pdotforms/fact_sheets/fs-pub7212.pdf. Accessed 13 Jan 2012

Aspinall PA et al (2008) Evaluation of quality of life and priorities of patients with glaucoma. Invest Ophthalmol Vis Sci 49(5):1907–1915

Atienza AA et al (2011) Self-reported and objectively measured activity related to biomarkers using NHANES. Med Sci Sports Exerc 43(5):815–821

Ball K et al (1993) Visual attention problems as a predictor of vehicle crashes in older drivers. Invest Ophthalmol Vis Sci 34(11):3110–3123

Banaszak-Holl J et al (2004) Predicting nursing home admission: estimates from a 7-year follow-up of a nationally representative sample of older Americans. Alzheimer Dis Assoc Disord 18(2):83–89

Bhargava JS et al (2006) Views of glaucoma patients on aspects of their treatment: an assessment of patient preference by conjoint analysis. Invest Ophthalmol Vis Sci 47(7):2885–2888

Bijnen FC et al (1998) Physical activity and 10-year mortality from cardiovascular diseases and all causes: the Zutphen Elderly Study. Arch Intern Med 158(14): 1499–1505

Black AA et al (2008) Visual impairment and postural sway among older adults with glaucoma. Optom Vis Sci 85(6):489–497

Black AA, Wood JM, Lovie-Kitchin JE (2011) Inferior field loss increases rate of falls in older adults with glaucoma. Optom Vis Sci 88(11):1275–1282

Bramley T et al (2008) Impact of vision loss on costs and outcomes in Medicare beneficiaries with glaucoma. Arch Ophthalmol 126(6):849–856

Broman AT et al (2002) The impact of visual impairment and eye disease on vision-related quality of life in a Mexican-American population: proyecto VER. Invest Ophthalmol Vis Sci 43(11):3393–3398

Broman AT et al (2008) Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from cross-sectional data. Invest Ophthalmol Vis Sci 49(1):66–76

Brusini P, Johnson CA (2007) Staging functional damage in glaucoma: review of different classification methods. Surv Ophthalmol 52(2):156–179

Burr JM et al (2007) Developing a preference-based glaucoma utility index using a discrete choice experiment. Optom Vis Sci 84(8):797–808

Clay OJ et al (2005) Cumulative meta-analysis of the relationship between useful field of view and driving performance in older adults: current and future implications. Optom Vis Sci 82(8):724–731

Coeckelbergh TRM et al (2002) The effect of visual field defects on driving performance: a driving simulator study. Arch Ophthalmol 120(11):1509–1516

Coleman AL (2007) Sources of binocular suprathreshold visual field loss in a cohort of older women being followed for risk of falls (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 105: 312–329

Colón-Emeric CS et al (2003) Risk factors for hip fracture in skilled nursing facilities: who should be evaluated? Osteoporos Int 14(6):484–489

Crabb DP et al (2004) A practical approach to measuring the visual field component of fitness to drive. Br J Ophthalmol 88(9):1191–1196

Cummings SR et al (1985) Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 7:178–208

Dhital A, Pey T, Stanford MR (2010) Visual loss and falls: a review. Eye (Lond) 24(9):1437–1446

Dougherty BE et al (2009) Development of a battery of functional tests for low vision. Optom Vis Sci 86(8): 955–963
Duthie A, Chew D, Soiza RL (2011) Non-psychiatric comorbidity associated with Alzheimer's disease. QJM 104(11):913–920
Eberhard JW (1998) Driving is transportation for most older adults. Geriatrics 53(Suppl 1):S53–S55
Eichenbaum JW et al (1999) The prevalence of eye disease in nursing home and non-nursing home geriatric populations. Arch Gerontol Geriatr 28(3):191–204
Emerson JL et al (2011) Predictors of driving outcomes in advancing age. Psychol Aging. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22182364. Accessed 13 Jan 2012
Esterman B (1982) Functional scoring of the binocular field. Ophthalmology 89(11):1226–1234
Fortenbaugh FC et al (2007) Losing sight of the bigger picture: peripheral field loss compresses representations of space. Vision Res 47(19):2506–2520
Freeman EE et al (2006) Driving status and risk of entry into long-term care in older adults. Am J Public Health 96(7):1254–1259
Freeman EE et al (2007) Visual field loss increases the risk of falls in older adults: the Salisbury Eye Evaluation. Invest Ophthalmol Vis Sci 48(10): 4445–4450
Freeman EE et al (2008) Glaucoma and quality of life: the Salisbury Eye Evaluation. Ophthalmology 115(2): 233–238
Friedman DS et al (2007) Glaucoma and mobility performance: the Salisbury Eye Evaluation Project. Ophthalmology 114(12):2232–2237
Garatachea N et al (2009) Feelings of well being in elderly people: relationship to physical activity and physical function. Arch Gerontol Geriatr 48(3):306–312
Gilhotra JS et al (2001) Impaired vision and other factors associated with driving cessation in the elderly: the Blue Mountains Eye Study. Clin Experiment Ophthalmol 29(3):104–107
Gutierrez P et al (1997) Influence of glaucomatous visual field loss on health-related quality of life. Arch Ophthalmol 115(6):777–784
Haymes SA et al (2007) Risk of falls and motor vehicle collisions in glaucoma. Invest Ophthalmol Vis Sci 48(3):1149–1155
Hodapp E, Parrish R, Anderson D (1993) Clinical decisions in glaucoma. Mosby, St Louis
Hu PS et al (1998) Crash risks of older drivers: a panel data analysis. Accid Anal Prev 30(5):569–581
Jampel HD, Friedman DS et al (2002a) Correlation of the binocular visual field with patient assessment of vision. Invest Ophthalmol Vis Sci 43(4):1059–1067
Jampel HD, Schwartz A et al (2002b) Glaucoma patients' assessment of their visual function and quality of life. J Glaucoma 11(2):154–163
Janz NK et al (2001) The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. Ophthalmology 108(11):1954–1965
Janz NK et al (2009) Evaluating clinical change and visual function concerns in drivers and nondrivers with glaucoma. Invest Ophthalmol Vis Sci 50(4): 1718–1725
Johnson CA, Keltner JL (1983) Incidence of visual field loss in 20,000 eyes and its relationship to driving performance. Arch Ophthalmol 101(3):371–375
Kaplan GA et al (1987) Mortality among the elderly in the Alameda County Study: behavioral and demographic risk factors. Am J Public Health 77(3): 307–312
Keay L et al (2009) Urban and rural differences in older drivers' failure to stop at stop signs. Accid Anal Prev 41(5):995–1000
Klein BE et al (1998) Performance-based and self-assessed measures of visual function as related to history of falls, hip fractures, and measured gait time. The Beaver Dam Eye Study. Ophthalmology 105(1): 160–164
Kotecha A et al (2009) The functional consequences of glaucoma for eye-hand coordination. Invest Ophthalmol Vis Sci 50(1):203–213
Kuyk T, Elliott JL, Fuhr PS (1998) Visual correlates of obstacle avoidance in adults with low vision. Optom Vis Sci 75(3):174–182
Lamoureux EL et al (2008) Visual impairment, causes of vision loss, and falls: the Singapore Malay eye study. Invest Ophthalmol Vis Sci 49(2):528–533
Lee BL et al (1998) The Glaucoma Symptom Scale. A brief index of glaucoma-specific symptoms. Arch Ophthalmol 116(7):861–866
Lee HC et al (2003) Using a driving simulator to identify older drivers at inflated risk of motor vehicle crashes. J Safety Res 34(4):453–459
Leske MC et al (2001) Incidence of open-angle glaucoma: the Barbados Eye Studies. The Barbados Eye Studies Group. Arch Ophthalmol 119(1):89–95
Lorenzana L et al (2009) A new method of assessing ability to perform activities of daily living: design, methods and baseline data. Ophthalmic Epidemiol 16(2): 107–114
Lynch BM et al (2008) Prospective relationships of physical activity with quality of life among colorectal cancer survivors. J Clin Oncol 26(27):4480–4487
Mangione CM et al (1992) Development of the "Activities of Daily Vision Scale". A measure of visual functional status. Med Care 30(12):1111–1126
Mangione CM et al (1998) Identifying the content area for the 51-item National Eye Institute Visual Function Questionnaire: results from focus groups with visually impaired persons. Arch Ophthalmol 116(2): 227–233
Mangione CM et al (2001) Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 119(7):1050–1058
Marottoli RA et al (1997) Driving cessation and increased depressive symptoms: prospective evidence from the New Haven EPESE. Established Populations for Epidemiologic Studies of the Elderly. J Am Geriatr Soc 45(2):202–206

McGwin G Jr, Owsley C, Ball K (1998) Identifying crash involvement among older drivers: agreement between self-report and state records. Accid Anal Prev 30(6):781–791

McGwin G Jr et al (2004) Is glaucoma associated with motor vehicle collision involvement and driving avoidance? Invest Ophthalmol Vis Sci 45(11):3934–3939

McGwin G Jr et al (2005) Visual field defects and the risk of motor vehicle collisions among patients with glaucoma. Invest Ophthalmol Vis Sci 46(12):4437–4441

McKean-Cowdin R et al (2007) Severity of visual field loss and health-related quality of life. Am J Ophthalmol 143(6):1013–1023

Medeiros FA et al (2011) Driving simulation as a performance-based test of visual impairment in glaucoma. J Glaucoma. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21467952. Accessed 13 Jan 2012

Mills RP (1998) Correlation of quality of life with clinical symptoms and signs at the time of glaucoma diagnosis. Trans Am Ophthalmol Soc 96:753–812

Mills RP et al (2001) Correlation of visual field with quality-of-life measures at diagnosis in the Collaborative Initial Glaucoma Treatment Study (CIGTS). J Glaucoma 10(3):192–198

Mills RP et al (2006) Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol 141(1):24–30

Mukesh BN et al (2002) Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology 109(6):1047–1051

Musch DC et al (1999) The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. Ophthalmology 106(4):653–662

Nelson P, Aspinall P, O'Brien C (1999) Patients' perception of visual impairment in glaucoma: a pilot study. Br J Ophthalmol 83(5):546–552

Nelson P et al (2003) Quality of life in glaucoma and its relationship with visual function. J Glaucoma 12(2):139–150

Nelson-Quigg JM, Cello K, Johnson CA (2000) Predicting binocular visual field sensitivity from monocular visual field results. Invest Ophthalmol Vis Sci 41(8):2212–2221

O'Hare F et al (2009) Readability of prescription labels and medication recall in a population of tertiary referral glaucoma patients. Clin Experiment Ophthalmol 37(9):849–854

Okonkwo OC et al (2008) Visual attention and self-regulation of driving among older adults. Int Psychogeriatr 20(1):162–173

Owsley C et al (2009) Characteristics of low-vision rehabilitation services in the United States. Arch Ophthalmol 127(5):681–689

Parrish RK 2nd et al (1997) Visual function and quality of life among patients with glaucoma. Arch Ophthalmol 115(11):1447–1455

Patel I et al (2006) Measures of visual function and percentage of preferred walking speed in older adults: the Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci 47(1):65–71

Quigley HA, Broman AT (2006) The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 90(3):262–267

Ragland DR, Satariano WA, MacLeod KE (2005) Driving cessation and increased depressive symptoms. J Gerontol A Biol Sci Med Sci 60(3):399–403

Ramulu PY et al (2009a) Driving cessation and driving limitation in glaucoma: the Salisbury Eye Evaluation Project. Ophthalmology 116(10):1846–1853

Ramulu PY et al (2009b) Glaucoma and reading speed: the Salisbury Eye Evaluation project. Arch Ophthalmol 127(1):82–87

Ramulu PY et al (2011) Comparison of home and away-from-home physical activity using accelerometers and cellular network-based tracking devices. J Phys Act Health. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21952052. Accessed 22 Nov 2011

Ramulu PY et al (2012a) Real-world assessment of physical activity in glaucoma using an accelerometer. Ophthalmology 119(6):1159–1166

Ramulu PY et al (2012b) Fear of falling and visual field loss from glaucoma. Ophthalmology 119(7):1352–1358

Rubin GS et al (2007) A prospective, population-based study of the role of visual impairment in motor vehicle crashes among older drivers: the SEE study. Invest Ophthalmol Vis Sci 48(4):1483–1491

Shabana N et al (2005) Postural stability in primary open angle glaucoma. Clin Experiment Ophthalmol 33(3):264–273

Skalicky S, Goldberg I (2008) Depression and quality of life in patients with glaucoma: a cross-sectional analysis using the Geriatric Depression Scale-15, assessment of function related to vision, and the Glaucoma Quality of Life-15. J Glaucoma 17(7):546–551

Smith ND, Crabb DP, Garway-Heath DF (2011) An exploratory study of visual search performance in glaucoma. Ophthalmic Physiol Opt 31(3):225–232

Susanna R Jr, Vessani RM (2009) Staging glaucoma patient: why and how? Open Ophthalmol J 3:59–64

Szlyk JP et al (2002) Driving performance in patients with mild to moderate glaucomatous clinical vision changes. J Rehabil Res Dev 39(4):467–482

Szlyk JP et al (2005) Driving performance of glaucoma patients correlates with peripheral visual field loss. J Glaucoma 14(2):145–150

Turano KA, Rubin GS, Quigley HA (1999) Mobility performance in glaucoma. Invest Ophthalmol Vis Sci 40(12):2803–2809

van Gestel A et al (2010) The relationship between visual field loss in glaucoma and health-related quality-of-life. Eye (Lond) 24(12):1759–1769

van Landingham SW et al (2012) Visual field loss and accelerometer-measured physical activity in the United States 119(12):2486–2492

van Landingham SW et al (2013) Driving patterns in older adults with glaucoma. BMC Ophthalmol 13(1):4

Viswanathan AC et al (1999) Severity and stability of glaucoma: patient perception compared with objective measurement. Arch Ophthalmol 117(4): 450–454

West SK, Munoz B et al (1997a) Function and visual impairment in a population-based study of older adults. The SEE project. Salisbury Eye Evaluation. Invest Ophthalmol Vis Sci 38(1):72–82

West SK, Rubin GS et al (1997b) Assessing functional status: correlation between performance on tasks conducted in a clinic setting and performance on the same task conducted at home. The Salisbury Eye Evaluation Project Team. J Gerontol A Biol Sci Med Sci 52(4):M209–M217

West SK et al (2010) Older drivers and failure to stop at red lights. J Gerontol A Biol Sci Med Sci 65(2): 179–183

Yu MSW, Chan CCH, Tsim RKM (2007) Usefulness of the Elderly Mobility Scale for classifying residential placements. Clin Rehabil 21(12):1114–1120

# 12 Impact of Early and Late Age-Related Macular Degeneration on Quality of Life

Robert P. Finger, Eva Fenwick,
and Ecosse L. Lamoureux

## 12.1 Introduction

The impact of early and late age-related macular degeneration (AMD) on quality of life (QoL) has been comprehensively assessed to date (Lamoureux et al. 2011; Wong et al. 2004; Espallargues et al. 2005; Finger et al. 2011a; Mangione et al. 1999). Early stages of the disease are associated with little functional loss (i.e. normal visual acuity) and few symptoms. However, the prognosis is poor for most patients affected by either atrophic or neovascular late-stage AMD. In the late-stage condition, central vision can be severely impaired, leading to a central scotoma. The implications of this level of visual impairment on daily functioning activities include inability to read, watch TV, recognise faces or do manual work requiring near central vision (Birk et al. 2004). Vision impairment associated with AMD also impacts on falls, mobility and emotional well-being (Parrish et al. 1997; Mackenzie et al. 2002). However, to understand the impact of AMD on QoL, it is important to consider vision loss not in isolation, but in the context of a patient's ability to adapt and cope (Slakter and Stur 2005). For example, functional difficulties can be partly alleviated by using magnifying glasses, screen-projection devices such as CCTVs and other low-vision aids and devices. Despite this, patients with late-stage AMD remain severely limited in undertaking many everyday activities. As highlighted in previous chapters (e.g. Chap. 3), the incidence of AMD is projected to increase due to current demographic trends, but less cases may progress to the more severe late stages due to treatment and other unknown factors in high-income countries. Thus, a large proportion of the elderly population is likely to experience serious QoL detriments associated with AMD.

This chapter summarises the current literature regarding the impact of early and late AMD on various aspects of QoL. Due to the magnitude of available information, this chapter is not designed to be all encompassing or to provide an exhaustive review of the current and historical literature related to this topic. Rather, it provides an overview of the key research in this area. As QoL impact and severity of AMD are correlated, we discuss early- and late-stage AMD and their

R.P. Finger (✉)
Centre for Eye Research Australia,
Royal Victorian Eye and Ear Hospital,
University of Melbourne, Melbourne, Australia

Department of Ophthalmology,
University of Bonn, Bonn, Germany
e-mail: robert.finger@unimelb.edu.au

E. Fenwick
Centre for Eye Research Australia,
Royal Victorian Eye and Ear Hospital,
University of Melbourne, Melbourne, Australia

E.L. Lamoureux
Centre for Eye Research Australia,
Royal Victorian Eye and Ear Hospital,
University of Melbourne, Melbourne, Australia

Singapore Eye Research Institute,
National University of Singapore, Singapore, Singapore

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_12, 

impact on QoL separately in this chapter. First, however, we assess the emerging field of outcomes assessment and discuss the merits of currently available patient-reported outcome measures in AMD research. Second, the impact of early and late AMD on QoL and the effect of treatment for late AMD on its QoL impact are depicted. The chapter concludes with an outlook on future developments in this area of research.

## 12.2 Measuring Quality of Life in AMD

To date, there is no consensus of a common definition of QoL. The majority of definitions use a multidimensional construct, including a physical dimension (disease symptoms and their treatment), a functional dimension (self-care, mobility, activity level and activities of daily living), a social dimension (social contact and interpersonal relationships) and a psychological dimension (cognitive function, emotional status, well-being, satisfaction and happiness) (Aaronson 1988). Generic or health-related QoL (HRQoL) instruments tend to include items in all four domains without little or no relevance to vision (de Boer et al. 2004). Vision-related QoL (VRQoL) instruments tend to include items in all four domains as well, but with a focus on the impact of vision and its impairment on QoL. A subset of instruments focuses on the functional impact of vision impairment, with a number of items assessing vision-specific functioning (VF).

There is a growing body of evidence demonstrating the considerable impact of AMD, particularly in its late stages on vision-specific functioning (VF), and vision- and health-related quality of life (VR and HRQoL) using a number of patient-reported outcome measures (PROs) (Finger et al. 2008a; Scott et al. 1999; Weih et al. 2002). Patient-reported outcomes, especially QoL, have been met with increasing interest over the last two decades. A recent statement by the Food and Drug Administration (FDA) of the United States assigned QoL a similar status to efficacy in the drug regulatory process (O'Shaughnessy et al. 1991). This is not yet the case in Europe, where safety and efficacy remain the sole criteria for drug approval. However, the European Agency for the Evaluation of Medicinal Products (EMEA) has also recently acknowledged the increasing importance of QoL in the drug regulatory process (Committee for Medicinal Products for Human Use 2005; Chassany et al. 2002). Furthermore, a growing need to explain the results of clinical studies in the metric of everyday patient functioning has further advanced the use of PROs (Mangione et al. 1999).

The use of PROs or questionnaires to assess the impact of vision impairment from the patient's perspective is now common in ophthalmic research and clinical practice (Finger et al. 2008b). As VRQoL is a complex, multidimensional concept, few PROs are true QoL instruments. Some questionnaires purely assess VF (e.g. the Visual Function Index – 14 items; VF-14), whereas others have been designed to capture the impact of visual impairment on aspects of QoL beyond VF, such as participation, and social and emotional well-being (e.g. the Impact of Vision Impairment (IVI) or the Daily Living Tasks Dependent on Vision (DLTV)). Generic HRQoL PROs such as the SF-36 have also been used to assess the QoL impact of AMD. However, while the use of generic tools can be important to delineate the impact of non-ocular conditions on QoL (Finger et al. 2011b), this chapter focuses solely on vision-specific PROs as these are most sensitive to the vision-specific impairment associated with AMD. Overall, it is important to note that all PROs remain approximations of QoL. As measures of VF and QoL correlate most highly with the visual acuity of the better-seeing eye, this clinical outcome is most commonly used in VF and QoL research. Binocular visual acuity, which best reflects daily vision, is also often measured.

A large number of PROs are available to measure VRQoL, HRQoL, VF and other outcomes in AMD (Finger et al. 2008a). To ensure high-quality assessments and correct assumptions based on gathered data, psychometrically valid instruments are required (Lamoureux and Pesudovs 2011). Commonly, patients are asked to rate the impact of their vision impairment

(if any) or ocular condition on various underlying traits such as mobility, activity limitation, reading and accessing information or emotional well-being using a set of relevant items (questions) (Pesudovs et al. 2007). Alternatively, patients may also be required to rate not only their impairment but also the importance of each item. These ratings are then multiplied (impairment × importance) to arrive at an individually weighted impact score (Mitchell and Bradley 2004; Scheibler et al. 2010). One questionnaire using a multiplicative rating scale specifically designed to measure VRQoL in macular diseases such as AMD is the Macular Disease Quality of Life questionnaire (MacDQoL) (Mitchell and Bradley 2004; Mitchell et al. 2005). However, there are various limitations associated with the MacDQoL when used in this way which are discussed in Sect. 2.1, and recommendations for the usage of this instrument are provided.

An instrument's ability to capture differences in disease severity and response to treatment (i.e. its discriminant ability) is a crucial characteristic, especially when using PROs as outcome measures of clinical trials. However, discriminant validity is rarely reported in studies using PROs. For example, only 20 % of studies have reported discriminant ability for the National Eye Institute Visual Function Questionnaire (NEI-VFQ)-52, Activities of Daily Vision Scale (ADVS), IVI questionnaire and VF-14 (Finger et al. 2008a). Thus, it is important that the magnitude of a questionnaire's responsiveness is considered against the tested intervention and its expected magnitude of effect. To date, the magnitude of a clinically significant change in a questionnaire score has been reported only for the NEI-VFQ-25 (Lindblad and Clemons 2005) whose accuracy is controversial (Marella et al. 2010).

The psychometric properties of an instrument are also important. Psychometric evaluations have traditionally been based on classical test theory (CTT). However, CTT can have several erroneous assumptions due to the use of summary scoring. Rasch analysis, a form of Item Response Theory, has resolved some of the problems associated with CTT, and it is currently the preferred method to (re-)analyse an instrument's measurement characteristics. Rasch analysis is a modern psychometric method that mathematically describes the interaction between respondents and test items. The Rasch model states that the probability of a correct response is a logistic function of the difference between person ability (person measure) and item difficulty (item measure) and applies a strict model which the pattern of participants' responses should satisfy (Garamendi et al. 2006; Norquist et al. 2004; Pesudovs 2004, 2006). Estimates from matrices of response data based on the model are obtained, and raw ordinal scores are thus transformed into data that approximate interval-level measurement (expressed in log of the odds units or logits). The specific methodology employed has been described in detail elsewhere (Revicki and Cella 1997). Reassessing the psychometric properties of VRQoL instruments to confirm their reliability and validity has become an important recent development. To date, of the psychometric tools most commonly used in AMD research, the NEI-VFQ-25 (Massof and Fletcher 2001; Langelaan et al. 2007), IVI (Lamoureux et al. 2006, 2007a), DLTV, (Denny et al. 2007) VF-14, (Velozo et al. 2000) ADVS (Pesudovs et al. 2003) and Low Luminance Questionnaire (LLQ) (Finger et al. 2011c) have been reassessed and potentially improved using Rasch analysis. The IVI and the DLTV have been most consistently shown to perform well under Rasch analysis and to be responsive to a number of health states and clinical characteristics of AMD (Denny et al. 2007; Lamoureux et al. 2007b, 2008a).

### 12.2.1 The MacDQoL

Due to the variety of PROs available, choosing which one to use can be difficult. The MacDQoL has been designed to measure VRQoL in macular diseases, covering areas such as mobility, socio-emotional well-being and near tasks, e.g. reading. It starts with two overview items (general QoL and overall macular disease-specific QoL), followed by 23 items with both 'impairment' and 'importance' ratings, and finally an open-ended question eliciting impact not covered by the

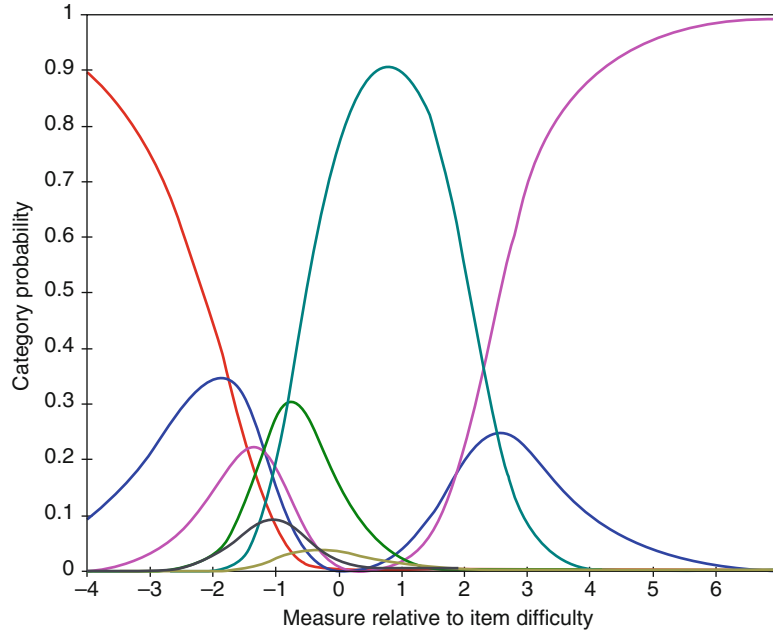


**Fig. 12.1** Category probability curves for all MacDQoL weighted response categories. Thresholds are disordered except for the two extreme response categories, and the *dark green curve* which peaks in the middle represents the score 0 which has a much higher probability than any other score. None of the other categories are likely to be chosen, leaving just the extreme categories and 0 as most likely to be observed, irrespective of respondents' location along the scale

structured questionnaire. Items are phrased 'If I had no macular disease, my… (e.g. family life) would be…': with five response categories for impairment (i.e. very much better, much better, a little better, the same, worse) and four for importance (i.e. very important, important, somewhat important, not at all important). All items excluding the two overview items, the final question and item 4 (work) are weighted by multiplying impairment and importance ratings (scored −3, −2, −1, 0, 1 and 3, 2, 1, 0, respectively) and calculating an average score. Its development was based on an existing instrument, the Audit of Diabetes-Dependent Quality of Life (the ADDQoL) as well as patient input (Mitchell and Bradley 2004). Using CTT, its main psychometric properties were assessed as satisfactory (Mitchell et al. 2005). However, there are important limitations associated with the MacDQoL which have been highlighted using Rasch analysis.

For example, recent work by our group has found that the MacDQoL fails to meet the criteria for a functioning scale when the suggested scoring algorithm is used. Item thresholds, which describe the item difficulty reflected in the response categories and how well an item matches levels of the measured construct, were severely disordered or overlapping beyond repair (Fig. 12.1), suggesting that respondents were unable to discriminate between the large number of response options required by the MacDQoL, thus demonstrating poor ability of the multiplicative rating scale to assess VRQoL. Omitting the importance rating and assessment of just the impairment scale also revealed issues with the response categories; however, after collapsing two response categories and utilising a four-point scale, these issues were resolved. Further assessment of the impairment scale of the MacDQoL demonstrated multidimensionality and a number of misfitting items, and the scale was split into an activity limitation and mobility and a socio-emotional well-being scale.

Our finding that the multiplicative rating scale of the MacDQoL was flawed is supported by similar study findings in which the poor functionality of other multiplicative rating scales has been demonstrated by Rasch analysis (Gothwal et al. 2011). These findings may be explained by considering the fundamental underlying assumptions of multiplicative rating scales employing impairment and importance ratings. First, such systems assume that patients can completely differentiate

between importance and difficulty. However, there is considerable evidence that importance is inherently incorporated into difficulty ratings and that patients cannot rate impairment or difficulty without incorporating the importance of the particular activity to them (Massof et al. 2005). Thus, every difficulty rating implicitly incorporates the respondent's importance rating.

The second assumption of multiplicative rating scales is that respondents can differentiate between the numerous response categories that result from multiplying the impairment and importance rating scales. In contrary, research into QoL measurement to date has shown that respondents can only differentiate between four to five response categories at most (Lissitz and Green 1975; Jenkins and Taber 1977). Thus, many of the response categories in multiplicative scales are underutilised, while some are overutilised as a result of the arithmetic required to derive the different response options (Pesudovs et al. 2003). Moreover, more than one pair of responses can lead to the same score which means the categories defy hierarchical ordering. Therefore, measurement precision is not increased by employing a large number of response categories (Lissitz and Green 1975; Jenkins and Taber 1977); indeed it is considerably decreased (Bond and Fox 2001).

Our findings indicate that the MacDQoL, a multiplicative scale, provides suboptimal measurement of VRQoL in noninterventional clinical trials or research involving interventions for AMD because its suggested scoring system is fundamentally flawed and, as such, is unlikely to provide a robust indication of treatment efficacy and may in fact result in findings that are attenuated compared to the true effect. Thus, researchers should consider using robust single scales instead (Gothwal et al. 2011). Nevertheless, most of the MacDQoL's major flaws can be remedied when using it as a non-multiplicative scale, i.e. by using only its impairment rating scale. However, QoL is an inherently multidimensional concept, and it is rarely useful to summarise QoL measurement with a single number, as this contributes to loss of information and measurement imprecision. Consequently, splitting its impairment scale into two separate scales, namely, activity limitation and mobility and socio-emotional well-being, represents the most optimal application of the MacDQoL.

While our results suggest the MacDQoL in its native form has no role in research studies where statistical averaging of multiple patients' data occurs, there may be other scenarios where its importance and impairment scales may be valuable. In daily clinical routine or in individual evaluation of interventions, especially rehabilitation, assessment of the importance of the tasks under question may be valuable. Therefore, selection of scales should be guided by the purpose of the intended measurement.

## 12.3 Impact of Early AMD on Quality of Life

Few studies have focused specifically on the impact of early AMD on QoL and VF. Early stages of the disease are usually symptom free, and visual acuity is good. Using various PROs, early AMD has repeatedly shown no association with decrements in VF or VRQoL. For example, a study by Lamoureux and colleagues found no difference in VF scores between persons with early AMD and persons without AMD in a population-based sample of the Singapore Malay Eye Study, using a Rasch-modified version of the VF-14 (VF-11) (Lamoureux et al. 2011). Similarly, clinic-based studies employing the ADVS (Mangione et al. 1999) and the MacDQoL (Mitchell et al. 2005) have demonstrated significantly greater impact on patients' VF and VRQoL in late AMD compared to early AMD. These findings suggest that early AMD has a relatively small impact on activities of daily living that require good vision. Considering that vision impairment is the principal contributor to poor visual functioning, this finding is not unexpected. Most VF and VRQoL instruments have been developed for use in visually impaired populations and may not be sensitive enough to pick up a decrement in visual functioning where there is no decrement in visual acuity and only some loss of scotopic vision or contrast sensitivity.

Once early AMD results in visual impairment, VF and VRQoL are impacted. We and others have previously reported that even mild visual impairment (0.3 < LogMAR < 0.5) has a significant and independent impact on vision-specific functioning (Finger et al. 2011a, d). While our sample was clinically based and moderate in size, this key finding is supported by three population-based studies. The Singapore Malay Eye Study (SiMES) found that unilateral mild vision loss or normal vision in one eye and low vision in the other were independently associated with poorer vision functioning (Lamoureux et al. 2008b). Similar findings were observed in two population-based cross-sectional eye health surveys conducted in Timor-Leste (du Toit et al. 2010) and in a Mexican-American population: the Proyecto VER (Broman et al. 2002).

Similarly, emotional well-being as part of VRQoL is affected in patients with even mild vision impairment (Finger et al. 2011a). This is important as evidence suggests that patients with vision impairment and emotional distress are likely to show increased functional disability independent of that caused by their vision impairment (Rovner et al. 1996, 2002; Rovner and Ganguli 1998). Depression is considered to result in functional decline in this group by reducing motivation, initiative and resiliency, (Rovner et al. 2002) and people with depression are less likely to access vision rehabilitation services than those not depressed (Tolman et al. 2005; Horowitz et al. 2003).

These findings are highly relevant to eye health professionals as they suggest that even patients at the mild spectrum of vision loss, i.e. with early AMD, should be targeted for treatment or referral as early as possible to prevent deterioration in vision impairment and minimise the potential impact on their VRQoL. Similarly, intervention strategies aimed at patients with even mild vision impairment could substantially improve their daily functioning and emotional stability. Moreover, the common practice of deferring low-vision referrals until visual impairment becomes severe should be reviewed (Lamoureux et al. 2008c).

### 12.3.1 Low Luminance Visual Functioning

A hallmark of a decline of visual functioning in early AMD is various parameters of scotopic functioning, which is why persons affected by early AMD may report difficulties with visual activities at dusk or dawn or under difficult lighting conditions (Scilley et al. 2002). Using the ADVS scale, Owsley and colleagues found persons with early AMD, even with good visual acuity in the fellow eye, reported difficulty in night driving, near vision tasks and glare disability, which was related to scotopic dysfunction measured as scotopic light sensitivity, compared with age-matched controls with good retinal health (Scilley et al. 2002). Night driving was the activity most affected. The common clinical notion that performance of most activities of daily life is unaffected "as long as a patient has one good eye" seems to be somewhat undermined by this finding as patients with only one eye affected by early AMD had difficulties noteworthy enough to report (Scilley et al. 2002). The work by Owsley and co-workers (Scilley et al. 2002) on the impact of different lighting conditions on AMD patients' visual functioning led them to develop the Low Luminance Questionnaire (LLQ) to measure the impact of mesopic (intermediate levels of illumination) and scotopic (low levels of illumination) vision impairment on VF (Owsley et al. 2006a). The LLQ has been shown to be internally valid and reliable (Owsley et al. 2006a) and responsive to interventions (Owsley et al. 2006b).

We investigated the relationship between vision impairment and low luminance functioning in a clinical sample of German outpatients (Finger et al. 2011c). We first assessed the psychometric properties of the German version of the LLQ (30 items) using Rasch analysis. After collapsing disordered thresholds and removing seven misfitting items, we found the LLQ-23 to be a valid, reliable and unidimensional scale to assess low luminance functioning (Finger et al. 2011c). Further analyses showed that vision impairment, AMD, cataract and poorer self-reported health were associated with poorer low

luminance functioning. Even at mild levels of vision impairment, participants reported poor low luminance functioning (Finger et al. 2011c).

Our finding of an independent association of retinal diseases such as AMD with low luminance functioning is not unexpected (Mangione et al. 1999, 2001; Scilley et al. 2002; Owsley et al. 2006a, b, 2007; Ying et al. 2008). Owsley and associates found that low luminance functioning as assessed by the LLQ was more responsive to changes in rod-mediated dark adaptation in AMD than general vision-specific functioning as assessed by the NEI-VFQ (Owsley et al. 2007). Furthermore, patients in this study reported greater impact on low luminance functioning than vision-specific functioning in daytime conditions (Owsley et al. 2007). Our finding that ocular conditions such as AMD were independently associated with poor low luminance functioning underlines that visual functions such as contrast sensitivity and mesopic and scotopic function may be as important as visual acuity in determining patients' level of functional disability. Controlling for conventional visual functioning (VF-14 scores), the only other ocular condition found to be associated with low luminance VRQoL in our study was cataract (Finger et al. 2011c).

However, few PROs (with the exception of some glaucoma-specific scales) sufficiently capture functioning in difficult lighting conditions. Depending on the intended purpose of measurement, additional PROs or items may need to be employed to capture decrements in VF and VRQoL in retinal diseases in their early stages where there is little or no visual impairment under standard (photopic) assessment conditions.

## 12.4 Impact of Late AMD on Quality of Life

Late AMD is characterised by either photoreceptor cell death in atrophic (dry) late-stage AMD or by destructive choroidal neovascularisation with subsequent oedema, haemorrhage and scarring in neovascular (wet) late-stage AMD. Both late stages almost always result in moderate to severe central visual acuity loss. The impact of late AMD on VF and VRQoL is considerable. However, most studies have demonstrated that decline in VF and VRQoL caused by late AMD is a function of the visual impairment it causes. A number of population-based and clinic-based studies have found that late AMD is not independently associated with VF when visual acuity or present vision impairment is controlled for (Lamoureux et al. 2011; Mangione et al. 1999). Similarly, using utilities elicited from patients with the time-trade-off method, Brown and coworkers showed that similar levels of visual loss in diabetic retinopathy and AMD caused similar disutility, emphasising that patient-reported utility (and QoL) scores are related more to the level of vision impairment than to the underlying cause of vision loss (Brown et al. 2002). Severe visual impairment has been associated with higher levels of depression (Brody et al. 2001), greater life stress, lower satisfaction and activity levels (Brody et al. 1999) compared to none or mild levels of vision loss.

Patients with late AMD have reported greater life stress, lower satisfaction and lower activity levels than controls (Brody et al. 1999). Moreover, HRQoL in late AMD patients has been shown to be similar or even lower and emotional distress higher compared with other serious chronic health conditions such stroke or metastasised solid tumour (Williams et al. 1998). A qualitative study of patients with advanced AMD in Australia reported that people resist asking for help for fear of becoming a burden and go to great lengths to remain independent. This can lead to social isolation, itself a factor in the progression of depression and poor emotional well-being (Wong et al. 2004). Participants in this study also felt concerned about their 'understanding of their condition'. Focus groups in Sweden have also demonstrated a need for more information about AMD and its consequences to be provided to patients, including how to prepare for a life with severe visual impairment (Ivanoff et al. 1996).

Late-stage AMD usually occurs in one eye at a time. Progression from neovascular AMD in

one eye to binocular neovascular AMD leads to a substantial additional loss of VRQoL. Using the NEI-VFQ, progression to bilateral neovascular AMD led to a decrease of 6–10 points on the overall score, after adjusting for visual acuity and other factors (Dong et al. 2004). Similarly, loss of ability to perform specific activities, such as driving, is often associated with a considerable decrease in reported QoL. In the USA driving is an important daily activity for a large proportion of the population. In patients with AMD, even when the visual acuity level required for driving is maintained, difficulty with complex driving situations such as at night, in heavy traffic or in rain, are often reported (DeCarlo et al. 2003). Inability to perform important daily activities can lead to a considerable decrease in QoL. Key activities are likely to vary between countries and cultures. For example, while driving is extremely important in the USA and Australia, it is less important for a large proportion of the European elderly population, where many elderly women do not have a driver's licence.

Different measures of visual function beyond visual acuity, such as contrast sensitivity or depth perception, may also be important factors associated with performance of vision-related tasks and reported VRQoL in late AMD. Reduced visual acuity has been reported to be closely related with tasks involving good resolution and adaptation to changing light levels, whereas contrast sensitivity may be more closely associated with distance judgement, night driving (or other mobility-related activities at low-light levels) and overall mobility. Reduced visual acuity and contrast sensitivity were found to be significant risk factors for self-reported disability in patients with late AMD (Rubin et al. 1994).

In summary, there is little evidence to date that early AMD without associated visual impairment has a measurable effect on VF or VRQoL. While patients' emotional well-being may be temporarily affected at diagnosis, as long as function is not affected, patients are usually resilient and are able to fully cope with their condition (Knudtson et al. 2005). Once vision is impaired, however, associated decreases in VF and VRQoL are observed, irrespective of the underlying condition. Late AMD which is associated with central field loss and a reduction of visual acuity has a considerable impact on all domains of QoL. In particular reading or other activities which require high resolution and detail are adversely affected, which often leads to a considerable impact on various socio-emotional domains, anxiety and depression.

### 12.4.1 Impact of Treatment on QoL in Late AMD

To date, only neovascular (nv) late-stage AMD is amenable to treatment. Available treatment does not cure the disease but rather leads to stabilisation and possibly some improvement in visual acuity of the affected eye. A number of treatment options are available, some of which, namely, retinal laser coagulation or transpupillary thermal therapy, have been abandoned in the wake of newer and more effective treatments such as the current gold standard, intravitreal injections of anti-VEGF (vascular endothelial growth factor) agents (Finger et al. 2007).

There is little evidence for a positive effect of radiotherapy, submacular surgery or laser photocoagulation on VRQoL in nv AMD (Slakter and Stur 2005). Photodynamic therapy (PDT) has been reported to have a positive effect on reported utilities, with a 10 % increase in quality-adjusted life years over 2 years, given the assumption that the better-seeing eye was treated and had a baseline acuity of 20/40 (Sharma et al. 2001). Assessing vision and visual functioning after treatment with PDT for nv AMD, Armbrecht and co-workers reported that although there were significant decreases in some of the QoL items tested, patients were significantly less anxious and more independent outdoors at the 12-month follow-up (Armbrecht et al. 2004). However, PDT did not prevent further vision loss and, overall, reported QoL decreased when visual acuity decreased during follow-up (Armbrecht et al. 2004).

In large phase III clinical trials (combined $n > 1{,}000$), anti-VEGF treatment for nv AMD has been shown to improve reported VRQoL, regardless of whether the worse- or better-seeing eye

was treated over 24 months of regular monthly treatments (Bressler et al. 2010). Similarly, an increase in visual functioning and VRQoL, despite no improvement in binocular BCVA due to treatment of the worse eye, has been reported for other ophthalmic interventions, e.g. vitrectomy for macular holes or epiretinal membranes (Hirneiss et al. 2006, 2007). Other studies have shown less improvement in VRQoL with the same intervention outside highly standardised phase II or III clinical trials, where treatment was less intense (fewer injections) and VRQoL could only be maintained but not improved (Finger et al. WAVE-study, manuscript under review). Whether the demonstrated positive effect of anti-VEGF treatment on VRQoL can be maintained beyond 2 years, and to what extent, remains uncertain. As highlighted above, reported QoL is closely related to current vision, and thus any treatment which improves or maintains vision is expected to have some impact on reported QoL.

## Conclusions

AMD has a profound effect on patients' VF and VRQoL especially once the disease has progressed to its late stages such as nv AMD. In early AMD, where visual acuity loss is absent or minimal, VF and VRQoL may also be affected due to poor contrast sensitivity, poor adaptation to low and changing light levels or poor mesopic sensitivity although this has not been detected by the majority of available PROs to date. Mild visual impairment can lead to a clinically meaningful reduction in VF and VRQoL. A reduction in both visual acuity and contrast sensitivity in AMD patients is unequivocally associated with visual disability. Late stages of the disease considerably impact VF and VRQoL, with reading and activities requiring seeing detail as well as socio-emotional domains being most severely affected. Visual impairment associated with AMD is also a risk factor for depression. Treatment for AMD has been shown to lead to an improvement in VRQoL if vision is improved. However, almost all instruments still lack information as to how precise they capture a change over time and information about the magnitude of a change in the instrument's score that is considered clinically meaningful. Once these aspects have been established for commonly used instruments, they will very likely become part of the standard outcome measures used in clinical research and required by regulatory authorities.

Assessing the impact of disease from the patient's perspective is gaining momentum, especially given the ageing population and the resulting increases in prevalence of AMD and related vision impairment. The use of psychometrically valid PROs is rapidly increasing with numerous tools becoming available. However, the applicability and appropriateness of available PROs requires careful evaluation prior to use. Psychometric measurement theory may be further advanced in the years to come, allowing for an even higher degree of standardisation and increased precision. Computer-adapted testing using item banks is a first step in this direction, (Lamoureux and Pesudovs 2011) and the first item banks will shortly become available for use in the major ocular conditions leading to visual impairment.

**Acknowlegments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable.

## References

Aaronson NK (1988) Quality of life: what is it? How should it be measured? Oncology (Williston Park) 2(5):69–76, 64

Armbrecht AM, Aspinall PA, Dhillon B (2004) A prospective study of visual function and quality of life following PDT in patients with wet age related macular degeneration. Br J Ophthalmol 88(10):1270–1273

Birk T, Hickl S, Wahl HW, Miller D, Kammerer A, Holz F et al (2004) Development and pilot evaluation of a psychosocial intervention program for patients with age-related macular degeneration. Gerontologist 44(6):836–843

Bond TG, Fox CM (2001) Applying the Rasch Model: fundamental measurement in the human sciences. Lawrence Erlbaum Associates, London

Bressler NM, Chang TS, Suner IJ, Fine JT, Dolan CM, Ward J et al (2010) Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. Ophthalmology 117(4):747–756 e4

Brody BL, Williams RA, Thomas RG, Kaplan RM, Chu RM, Brown SI (1999) Age-related macular degeneration: a randomized clinical trial of a self-management intervention. Ann Behav Med 21(4):322–329

Brody BL, Gamst AC, Williams RA, Smith AR, Lau PW, Dolnak D et al (2001) Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. Ophthalmology 108(10): 1893–1900; discussion 900–901

Broman AT, Munoz B, Rodriguez J, Sanchez R, Quigley HA, Klein R et al (2002) The impact of visual impairment and eye disease on vision-related quality of life in a Mexican-American population: proyecto VER. Invest Ophthalmol Vis Sci 43(11):3393–3398

Brown MM, Brown GC, Sharma S, Landy J, Bakal J (2002) Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. Arch Ophthalmol 120(4):481–484

Chassany O, Sagnier P, Marquis P, Fullerton S, Aaronson N (2002) Patient reported outcomes: the example of health-related quality of life – a European guidance document for the improved integration of health-related quality of life assessment in the drug regulatory process. Drug Inf J 36:209–238

Committee for Medicinal Products for Human Use (CHMP) (2005) Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. EMEA, London

de Boer MR, Moll AC, de Vet HC, Terwee CB, Volker-Dieben HJ, van Rens GH (2004) Psychometric properties of vision-related quality of life questionnaires: a systematic review. Ophthalmic Physiol Opt 24(4):257–273

DeCarlo DK, Scilley K, Wells J, Owsley C (2003) Driving habits and health-related quality of life in patients with age-related maculopathy. Optom Vis Sci 80(3): 207–213

Denny F, Marshall AH, Stevenson MR, Hart PM, Chakravarthy U (2007) Rasch analysis of the daily living tasks dependent on vision (DLTV). Invest Ophthalmol Vis Sci 48(5):1976–1982

Dong LM, Childs AL, Mangione CM, Bass EB, Bressler NM, Hawkins BS et al (2004) Health- and vision-related quality of life among patients with choroidal neovascularization secondary to age-related macular degeneration at enrollment in randomized trials of submacular surgery: SST report no. 4. Am J Ophthalmol 138(1):91–108

du Toit R, Palagyi A, Ramke J, Brian G, Lamoureux EL (2010) The impact of reduced distance and near vision on the quality of life of adults in Timor-Leste. Ophthalmology 117:2308–2314

Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA et al (2005) The impact of age-related macular degeneration on health status utility values. Invest Ophthalmol Vis Sci 46(11):4016–4023

Finger RP, Fleckenstein M, Scholl HP, Holz FG (2007) Therapeutic anti-VEGF in ophthalmology: physiopathology and treatment of age-related macular degeneration. Pharm Unserer Zeit 36(6):424–430

Finger RP, Fleckenstein M, Holz FG, Scholl HP (2008a) Quality of life in age-related macular degeneration: a review of available vision-specific psychometric tools. Qual Life Res 17(4):559–574

Finger RP, Scholl HP, Holz FG (2008b) "Patient reported outcomes" – Relevanz und Anwendung in der Augenheilkunde. Ophthalmologe 105(8):722–726

Finger RP, Fenwick E, Marella M, Dirani M, Holz FG, Chiang PP et al (2011a) The impact of vision impairment on vision-specific quality of life in Germany. Invest Ophthalmol Vis Sci 52(6):3613–3619

Finger RP, Fenwick E, Marella M, Charbel Issa P, Scholl HP, Holz FG et al (2011b) The relative impact of vision impairment and cardiovascular disease on quality of life: the example of pseudoxanthoma elasticum. Health Qual Life Outcomes 9(1):113

Finger RP, Fenwick E, Owsley C, Holz FG, Lamoureux EL (2011c) Visual functioning and quality of life under low luminance: evaluation of the German Low Luminance Questionnaire. Invest Ophthalmol Vis Sci 52(11):8241–8249

Finger RP, Fenwick E, Chiang PP, Petrak M, Holz FG, Marella M et al (2011d) The impact of the severity of vision loss on vision-specific functioning in a German outpatient population – an observational study. Graefes Arch Clin Exp Ophthalmol 249(8):1245–1253

Garamendi E, Pesudovs K, Stevens MJ, Elliott DB (2006) The Refractive Status and Vision Profile: evaluation of psychometric properties and comparison of Rasch and summated Likert-scaling. Vision Res 46:1375–1383

Gothwal VK, Wright TA, Lamoureux EL, Pesudovs K (2011) Multiplicative rating scales do not enable measurement of vision-related quality of life. Clin Exp Optom 94(1):52–62

Hirneiss C, Rombold F, Kampik A, Neubauer AS (2006) Visual quality of life after vitreoretinal surgery for epiretinal membranes. Ophthalmologe 103(2): 109–113

Hirneiss C, Neubauer AS, Gass CA, Reiniger IW, Priglinger SG, Kampik A et al (2007) Visual quality of life after macular hole surgery: outcome and predictive factors. Br J Ophthalmol 91(4):481–484

Horowitz A, Reinhardt JP, Boerner K, Travis LA (2003) The influence of health, social support quality and rehabilitation on depression among disabled elders. Aging Ment Health 7(5):342–350

Ivanoff SD, Sjostrand J, Klepp KI, Lind LA, Lindqvist BL (1996) Planning a health education programme for the elderly visually impaired person – a focus group study. Disabil Rehabil 18(10):515–522

Jenkins GDJ, Taber TD (1977) A Monte-Carlo study of factors affecting three indices of composite scale reliability. J Appl Psychol 62:392–398

Knudtson MD, Klein BE, Klein R, Cruickshanks KJ, Lee KE (2005) Age-related eye disease, quality of life, and functional activity. Arch Ophthalmol 123(6):807–814

Lamoureux E, Pesudovs K (2011) Vision-specific quality-of-life research: a need to improve the quality. Am J Ophthalmol 151(2):195–197 e2

Lamoureux EL, Pallant JF, Pesudovs K, Hassell JB, Keeffe JE (2006) The impact of vision impairment questionnaire: an evaluation of its measurement properties using Rasch analysis. Invest Ophthalmol Vis Sci 47(11):4732–4741

Lamoureux EL, Pallant JF, Pesudovs K, Rees G, Hassell JB, Keeffe JE (2007a) The impact of vision impairment questionnaire: an assessment of its domain structure using confirmatory factor analysis and Rasch analysis. Invest Ophthalmol Vis Sci 48(3): 1001–1006

Lamoureux EL, Pallant JF, Pesudovs K, Rees G, Hassell JB, Keeffe JE (2007b) The effectiveness of low-vision rehabilitation on participation in daily living and quality of life. Invest Ophthalmol Vis Sci 48(4): 1476–1482

Lamoureux EL, Pallant JF, Pesudovs K, Tennant A, Rees G, O'Connor PM et al (2008a) Assessing participation in daily living and the effectiveness of rehabilitation in age related macular degeneration patients using the impact of vision impairment scale. Ophthalmic Epidemiol 15(2):105–113

Lamoureux EL, Chong E, Wang JJ, Saw SM, Aung T, Mitchell P et al (2008b) Visual impairment, causes of vision loss, and falls: the Singapore Malay eye study. Invest Ophthalmol Vis Sci 49(2):528–533

Lamoureux EL, Chong EW, Thumboo J, Wee HL, Wang JJ, Saw SM et al (2008c) Vision impairment, ocular conditions, and vision-specific function: the Singapore Malay Eye study. Ophthalmology 115(11): 1973–1981

Lamoureux EL, Mitchell P, Rees G, Cheung G, Yeo I, Lee SY et al (2011) Impact of early and late age-related macular degeneration on vision-specific functioning. Br J Ophthalmol 95(5):666–670

Langelaan M, van Nispen RM, Knol DL, Moll AC, de Boer MR, Wouters B et al (2007) Visual Functioning Questionnaire: reevaluation of psychometric properties for a group of working-age adults. Optom Vis Sci 84(8):775–784

Lindblad AS, Clemons TE (2005) Responsiveness of the National Eye Institute Visual Function Questionnaire to progression to advanced age-related macular degeneration, vision loss, and lens opacity: AREDS report no. 14. Arch Ophthalmol 123(9):1207–1214

Lissitz RW, Green SB (1975) The effect of the number of scale points in reliability: a Monte-Carlo approach. J Appl Psychol 60:10–13

Mackenzie PJ, Chang TS, Scott IU, Linder M, Hay D, Feuer WJ et al (2002) Assessment of vision-related function in patients with age-related macular degeneration. Ophthalmology 109(4):720–729

Mangione CM, Gutierrez PR, Lowe G, Orav EJ, Seddon JM (1999) Influence of age-related maculopathy on visual functioning and health-related quality of life. Am J Ophthalmol 128(1):45–53

Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD (2001) Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 119(7):1050–1058

Marella M, Pesudovs K, Keeffe JE, O'Connor PM, Rees G, Lamoureux EL (2010) The psychometric validity of the NEI VFQ-25 for use in a low-vision population. Invest Ophthalmol Vis Sci 51(6):2878–2884

Massof RW, Fletcher DC (2001) Evaluation of the NEI visual functioning questionnaire as an interval measure of visual ability in low vision. Vision Res 41(3):397–413

Massof RW, Hsu CT, Baker FH, Barnett GD, Park WL, Deremeik JT et al (2005) Visual disability variables. I: the importance and difficulty of activity goals for a sample of low-vision patients. Arch Phys Med Rehabil 86(5):946–953

Mitchell J, Bradley C (2004) Design of an individualised measure of the impact of macular disease on quality of life (the MacDQoL). Qual Life Res 13(6):1163–1175

Mitchell J, Wolffsohn JS, Woodcock A, Anderson SJ, McMillan CV, Ffytche T et al (2005) +Psychometric evaluation of the MacDQoL individualised measure of the impact of macular degeneration on quality of life. Health Qual Life Outcomes 3:25

Norquist JM, Fitzpatrick R, Dawson J, Jenkinson C (2004) Comparing alternative Rasch-based methods vs raw scores in measuring change in health. Med Care 42(1 Suppl):I25–I36

O'Shaughnessy JA, Wittes RE, Burke G, Friedman MA, Johnson JR, Niederhuber JE et al (1991) Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials. J Clin Oncol 9(12):2225–2232

Owsley C, McGwin G Jr, Scilley K, Kallies K (2006a) Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. Invest Ophthalmol Vis Sci 47(2):528–535

Owsley C, McGwin G, Jackson GR, Heimburger DC, Piyathilake CJ, Klein R et al (2006b) Effect of short-term, high-dose retinol on dark adaptation in aging and early age-related maculopathy. Invest Ophthalmol Vis Sci 47(4):1310–1318

Owsley C, McGwin G Jr, Jackson GR, Kallies K, Clark M (2007) Cone- and rod-mediated dark adaptation impairment in age-related maculopathy. Ophthalmology 114(9):1728–1735

Parrish RK, Gedde SJ, Scott IU, Feuer WJ, Schiffman JC, Mangione CM et al (1997) Visual function and quality of life among patients with glaucoma. Arch Ophthalmol 115(11):1447–1455

Pesudovs K (2004) Autorefraction as an outcome measure of laser in situ keratomileusis. J Cataract Refract Surg 30(9):1921–1928

Pesudovs K (2006) Patient-centred measurement in ophthalmology – a paradigm shift. BMC Ophthalmol 6(1):25

Pesudovs K, Garamendi E, Keeves JP, Elliott DB (2003) The Activities of Daily Vision Scale for cataract surgery outcomes: re-evaluating validity with Rasch analysis. Invest Ophthalmol Vis Sci 44(7):2892–2899

Pesudovs K, Burr JM, Harley C, Elliott DB (2007) The development, assessment, and selection of questionnaires. Optom Vis Sci 84(8):663–674

Revicki DA, Cella DF (1997) Health status assessment for the twenty-first century: item response theory, item banking and computer adaptive testing. Qual Life Res 6(6):595–600

Rovner BW, Ganguli M (1998) Depression and disability associated with impaired vision: the MoVIES project. J Am Geriatr Soc 46(5):617–619

Rovner BW, Zisselman PM, ShmuelyDulitzki Y (1996) Depression and disability in older people with impaired vision: a follow-up study. J Am Geriatr Soc 44(2):181–184

Rovner BW, Casten RJ, Tasman WS (2002) Effect of depression on vision function in age-related macular degeneration. Arch Ophthalmol 120(8):1041–1044

Rubin GS, Roche KB, Prasada-Rao P, Fried LP (1994) Visual impairment and disability in older adults. Optom Vis Sci 71(12):750–760

Scheibler F, Finger RP, Grosselfinger R, Dintsios CM (2010) Patient-reported and patient-weighted outcomes in ophthalmology. Ophthalmologe 107(3):235–240

Scilley K, Jackson GR, Cideciyan AV, Maguire MG, Jacobson SG, Owsley C (2002) Early age-related maculopathy and self-reported visual difficulty in daily life. Ophthalmology 109(7):1235–1242

Scott IU, Smiddy WE, Schiffman J, Feuer WJ, Pappas CJ (1999) Quality of life of low-vision patients and the impact of low-vision services. Am J Ophthalmol 128(1):54–62

Sharma S, Brown GC, Brown MM, Hollands H, Shah GK (2001) The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 108(11):2051–2059

Slakter JS, Stur M (2005) Quality of life in patients with age-related macular degeneration: impact of the condition and benefits of treatment. Surv Ophthalmol 50(3):263–273

Tolman J, Hill RD, Kleinschmidt JJ, Gregg CH (2005) Psychosocial adaptation to visual impairment and its relationship to depressive affect in older adults with age-related macular degeneration. Gerontologist 45(6):747–753

Velozo CA, Lai JS, Mallinson T, Hauselman E (2000) Maintaining instrument quality while reducing items: application of Rasch analysis to a self-report of visual function. J Outcome Meas 4(3):667–680

Weih LM, Hassell JB, Keeffe JE (2002) Assessment of the impact of vision impairment. Invest Ophthalmol Vis Sci 43(4):927–935

Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI (1998) The psychosocial impact of macular degeneration. Arch Ophthalmol 116(4):514–520

Wong EYH, Guymer RH, Hassell J, Keeffe J (2004) The experience of age-related macular degeneration. J Vis Imp Blind 98:629–640

Ying GS, Maguire MG, Liu C, Antoszyk AN (2008) Night vision symptoms and progression of age-related macular degeneration in the Complications of Age-related Macular Degeneration Prevention Trial. Ophthalmology 115(11):1876–1882

# Vision and Driving Performance in Elderly

13

Lisa Keay and Sheila K. West

## 13.1 Introduction

Older people are a large and growing sector of the driving population. In 2008, there were 32 million licensed drivers aged over 65 years in the USA. These drivers represent 15 % of all licensed drivers in the USA and are the fastest growing segment of the driving population (National Highway Traffic Safety 2009). Driving is the primary mode of transport for many older members of the population and facilitates the execution of routine daily activities, employment, and social interaction (Kostyniuk and Shope 2003). The capacity to drive a private motor vehicle is linked to being able to live independently in the community. Loss of driving privileges reduces out-of-home activity levels (Marottoli et al. 2000), is predictive or earlier admission to residential care (Freeman et al. 2006a), and increases prevalence of depressive symptoms (Dickerson et al. 2007). Though giving up driving is a major life event, surveys find that older drivers tend not to plan for driving cessation and are not familiar with alternative transport (Kostyniuk and Shope 2003). In a large survey in Michigan in the USA, two-thirds of survey respondents indicated that they would need to move from their home to a location with public or integrated transport if they could no longer drive (Kostyniuk and Shope 2003).

While there are clear benefits for mobility and community participation for older people who drive, concerns have been raised due to increased crash involvement and vulnerability to crash injury. Crash involvement per mile driven and likelihood for driver responsibility begins to increase from age 65 (Williams and Shabanova 2003), and by age 85, likelihood of crash involvement is approximately 2.5 times higher than that of the average driver (Cerrelli 2007). Unlike younger drivers whose higher crash rate is attributed to inexperience and risky driving behavior (Williams and Shabanova 2003), the high crash rate for older drivers is explained by a different set of factors. Crashes with older drivers are less likely to be associated with alcohol (National Highway Traffic Safety 2009), are more likely to be at intersections, and are associated with evaluation errors such as misjudging gaps in traffic (Ryan et al. 1998; Braitman et al. 2007).

Older people are also more likely to be seriously injured or to die as a result of a crash, and this is attributed in part to fragility of age (Meuleners et al. 2006; Hanrahan et al. 2009). In England, those aged 60 years and over account for 10 % of all road casualties but represent 26 % of all road fatalities (Department of the Environment Transport and the Regions United

L. Keay, BOptom, MPH, PhD (✉)
Division of Injury, The George Institute for Global Health, The University of Sydney, Sydney, Australia
e-mail: lkeay@georgeinstitute.org.au

S.K. West, PhD
Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_13, 

Kingdom 2000). A Canadian study has found age to be a significant factor increasing the severity of injuries in motor vehicle traffic crashes with those aged 80 years and over having the highest risk of being severely injured or dying as a result of a crash (Zhang et al. 2000). It is estimated that injury risk is nine times higher per mile driven in drivers 85 years and older compared to 25–69-year-olds (Li et al. 2003).

Age-related decline in physical, cognitive, and sensory function, including vision, has been proposed as the reason for poor driving performance and increased crash involvement among older drivers. Motivated by safety concerns, many researchers have investigated functional changes in older populations and the impact of these changes on driving (Table 13.1). However, it has also been proposed that older drivers lose their driving skills when they start to drive less (Langford et al. 2006). "The low mileage bias" may explain part of the increased crash risk or compound the effects of decline in function. Regardless of the mechanism, the larger number of older people who rely on driving for transport (Australian Bureau of Statistics 2008), the aging of the population in western countries (Statistics Portal 2007), and the increased risk of crash involvement and vulnerability to injury (Meuleners et al. 2006; Hanrahan et al. 2009; Lyman et al. 2002) make older driver safety a growing public health concern. The large volume of research into driving performance of older drivers and the role of functional loss has greatly informed our understanding of crash risk in this group.

## 13.2 Methods to Assess Driving Performance

### 13.2.1 On-Road Driving Assessment

An open- or closed-road driving assessment is the usual test of driving proficiency for new drivers to gain their license and in assessment of fitness to drive. On-road assessment has been used by a number of research groups to measure driving ability in older populations (Adrian et al. 2011; Wood 2002; Richardson and Marottoli 2003; Bowers et al. 2005; Bedard et al. 2011; Gstalter and Fastenmeier 2010; Dawson et al. 2010). In an on-road assessment, the test course is usually driven in a dedicated vehicle rather than the participants own vehicle with dual controls for safety during testing. Trained observers accompany the driver in the vehicle to score any errors as they happen, though some studies have used video data capture for subsequent analysis after completion of the trip (Adrian et al. 2011; Gstalter and Fastenmeier 2010; Dawson et al. 2010). The disadvantage of on-road testing is lack of familiarity with the vehicle and also the fact that drivers are evaluated on a test course, rather than on their own habitual driving routes. However, the number of errors in on-road assessment has been shown to be associated with self-reported crash involvement, providing supporting evidence for the relevance of on-road testing (Wood et al. 2009a).

### 13.2.2 Driving Simulators

Driving simulators are a laboratory-based method of assessing driving and involve interfacing programmable software to a driving cabin complete with accelerator, brake pedals and steering wheel, and projecting video of the computer-generated road environment at eye level. Steering movements and pedal displacements are measured during the driving sequences, and some systems include cameras to measure eye and head movements (Pradhan et al. 2005). These are intensive studies with relatively small sample sizes (Table 13.1). The advantage of simulator testing is that the driving situation can be finely controlled including audio distraction and variable complexity of the driving situation by changing presence of other vehicles and pedestrians and the road structure. All protocols usually involve a practice session before actual measurements commence. Two studies have compared simulator to on-road assessment and found results from the two methods to be positively associated (Lee et al. 2003) and to detect the same types of errors detected (Shechtman et al. 2009). A drawback for simulators is that they are expensive and need to be used in a dedicated laboratory. In addition, they may

**Table 13.1** Studies which have evaluated functional characteristics of older drivers and the relationship to driving performance or crash risk using test courses

| Study | Sample size | Age mean (range) | Outcome | Study findings |
|---|---|---|---|---|
| *On-road assessment* | | | | |
| Richardson and Marottoli (2003) | $n=35$ | 80 (70+) | Errors per drive | Visual attention (number cancellation task), visual memory (visual reproduction), and executive function (TMT Part B) were predictive of driving performance (adjusting for distance vision) |
| O'Connor et al. (2010) | $n=160$ | 78 (60+) | Errors per drive | Proposed a composite score which was predictive of driving performance including crash history, family concerns, clinical condition (medical issues which can impact vision included), and cognitive function |
| Dawson et al. (2010) | $n=111$<br>$n=80$ | 72 (65–89)<br>57 (40–64) | Errors per drive | This study found that a cognitive battery of 8 tests, UFOV, CS, VA, near VA, Structure from Motion, Functional Reach, Get-Up-and-Go, and Grooved Peg-board, was predictive of driving errors |
| Adrian et al. (2011) | $n=42$ | (60–82) | Errors per drive | This study found extraverted drivers had better driving performance (adjusting for cognitive function) |
| *Simulator studies* | | | | |
| Shanmugaratnam et al. (2010) | $n=18$<br>$n=18$ | 22 (<40)<br>65 (40+) | Driver control, errors, and attention/ reaction time | Advocates a battery of cognitive and psychomotor ability tests to assess fitness to drive |
| Park et al. (2011) | $n=48$<br>$n=55$ | 34 (25–45)<br>69 (65+) | Car crashes and driving errors | A computer-based battery of cognitive tests with pass/fail result was useful for predicting crash involvement and errors |
| Andrews and Westerman (2012) | $n=22$<br>$n=22$ | (26–40)<br>(60+) | Anticipating driving events, headway and lane position | Older drivers with higher cognitive ability anticipated traffic events more frequently |
| *Naturalistic driving* | | | | |
| West et al. (2010) | $n=1,425$ | 75 (67–87) | Not stopping at red traffic signals during 5-day period of monitoring | Reduced ability to pay attention to events in the vertical visual field (vertical AVF) was predictive of failing to stop at a red traffic light (models considered the effect of age, sex, race, education, health, visual and cognitive function) |
| Keay et al. (2009a) | $n=1,115$ | 78 (67–87) | Stopping at stop sign intersections during 5-day period of monitoring | Drivers resident in rural areas were less likely to comply to stopping. Drivers resident in urban areas who had visual field loss were more likely to stop suggesting cautious driving in those with field loss |
| Munro et al. (2010) | $n=1,080$ | 78 (67–88) | Lane change errors during 5-day period of monitoring | Poor cognition (attention and visual-motor integration) was related to lane change errors |
| *Crash involvement* | | | | |
| Ball et al. (1993) | $n=294$ | (55–90) | Self-reported at-fault police-attended crashes in last 5 years (confirmed by state records) | UFOV was independently predictive of crash risk (CS, peripheral VF and eye health, mental predicted score on UFOV) |

(continued)

**Table 13.1** (continued)

| Study | Sample size | Age mean (range) | Outcome | Study findings |
|---|---|---|---|---|
| Stutts et al. (1998) | $n=3,238$ | 74 (65+) | Crash involvement from state driver history file in 3 years prior to assessment | Cognitive test performance (TMT, Traffic Sign Recognition, reaction time) associated with modest increase in crash risk after adjusting for age, race, and driving exposure |
| Staplin et al. (2003) | $n=1,876$ | 68 (55–96) | 2-year self-reported crash involvement after assessment | The predictive value of screening tests (Motor-Free Visual Perception Test, TMT Part B, Delayed Recall, UFOV, Rapid Pace Walk, Head-Neck Rotation) declines within 2 years of assessment |
| Rubin et al. (2007) | $n=1,801$ | (65–84) | Involvement in crash according to the Maryland Automated Accident Report System in 5 years after assessment | Glare sensitivity, VF loss, and poor performance on UFOV were associated with crashes |
| Horswill et al. (2010) | $n=271$ | 75 (65–96) | Self-reported crash involvement in last 5 years | UFOV and hazard perception latency were both independently predictive of crash involvement (adjusting for age, sex, and driving exposure) |
| Meuleners et al. (2012) | $n=27,827$ | 60+ | Police-reported crash involvement | 13 % reduction in crash risk after cataract surgery adjusting for sociodemographic factors and comorbidities |

*HC* high contrast, *LC* low contrast, *VA* visual acuity, *CS* contrast sensitivity, *VF* visual field, *AVF* attentional visual field, *MOMSSE* Mattis Organic Mental Status Syndrome Examination, *BTA* Brief Test of Attention

not reflect an older driver's actual driving experience if she/he has limited their exposure to night driving or rush hour, for example.

### 13.2.3 Naturalistic Driving

Naturalistic driving or in-vehicle monitoring is being used increasingly in research into driver behavior. This is a product of reductions in cost and advances in Global Positioning Systems (GPS), data management, and telecommunications. Electronic data logging with GPS, video, and radars has now been used successfully in a number of studies (Porter and Whitton 2002; Baldwin et al. 2004; Niele et al. 2009) and shown to correlate well with self-report using driving diaries (Marshall et al. 2007). An early use of this technology described differences in speed and deceleration in young, middle-aged, and older drivers (Porter and Whitton 2002). The Salisbury Eye Evaluation Driving Study used a purpose built system (Baldwin et al. 2004) to assess driving in a cohort of drivers aged 67–87 and explored the visual and cognitive predictors of driving performance (Keay et al. 2009a; Munro et al. 2010; West et al. 2010). In-vehicle monitoring has had the most extensive application in the 100-Car study which was specifically designed to explore driver distraction (Dingus et al. 2006). This work is being extended into cohorts of older drivers (Antin 2010). Blanchard and colleagues (Blanchard and Myers 2010) have used a driving system to measure driving habits of older drivers including trip lengths, duration, and distance from home.

A driver monitoring system has advantages over other methods of driving assessment. Unlike in laboratory-based tests such as simulators, the duration of assessment can be much longer with some studies assessing driving for periods of 12 months (Dingus et al. 2006; Antin 2010). Further,

as the name "naturalistic driving" implies, there is less awareness of test conditions which could bias results. There are other applications of this technology such as integrated warning systems and interactive feedback for driver training (McLaughlin et al. 2008).

### 13.2.4 Crash Involvement

As crashes are rare events, large sample sizes are required for research studies evaluating crash risk. Future naturalistic driving studies with large enough periods of monitoring and sufficient sample sizes will be able to evaluate crashes and near-crashes objectively; however, without such capacity, crash involvement is collected either by self-report or state records. A number of studies with crash involvement at the outcome have relied on retrospective self-report of crash involvement during periods of between 2 and 5 years to increase the count of crashes (Staplin et al. 2003; Ball et al. 1993; Horswill et al. 2010; Stutts et al. 1998). Others have relied on state records of crashes (Rubin et al. 2007; Ball et al. 2010) or a combination of self-report and state records (Ball et al. 1993). McGwin et al. (1998) compared self-report to state records and finds significant underreporting (23 % of drivers) among drivers aged 55 years and older. Further, this analysis finds that investigations into the predictors of crash involvement showed differential results, depending on case definition. The restriction to at-fault crashes is a logical distinction, but in practice this process can be quite subjective.

Some examples of large administrative databases are the FARS (Fatality Analysis Reporting System http://www-fars.nhtsa.dot.gov/Main/index.aspx) which documents 30,000–40,000 fatal crashes each year in the USA. The main disadvantage of these data sets is that they lack detailed individual level data. Predictive factors which can be considered when analyzing these data sets are limited to variables such as previous driving citations (Bedard et al. 2008), type of crash (Braitman et al. 2007), and events which are recorded in hospital records such as cataract surgery (Meuleners et al. 2012). Data linkage has been used to evaluate crash involvement, combining large population-based travel surveys (Langford et al. 2006) or hospital records (Meuleners et al. 2012) to police crash records.

## 13.3 Jurisdictional Control: Who Can Drive?

Driving is a visually demanding activity, and most jurisdictions have minimum visual acuity requirements for driving. A 2005 review of vision testing for older driver licensing in several western jurisdictions (Australia, Canada, European Union, New Zealand, UK, USA) found similar criteria for visual acuity requiring 20/40–20/50 (6/12–6/15) and at least 120° horizontal visual field and some authorities specifying vertical visual field requirements (Bohensky et al. 2008). The implementation of these requirements varied widely particularly with regard to renewal periods and assessment of fitness to drive (Bohensky et al. 2008). A review of licensing policy and procedures (Dobbs 2008) found that age-triggered testing and shortening of the license renewal period for older drivers are not effective in reducing crashes but that in-person renewal showed some promise (Grabowski et al. 2004). Despite these regulations, surveys find 2.6 % of drivers have poor vision (6/12 or worse) and most of this is due to uncorrected refractive error (80 %) (Keeffe et al. 2002), highlighting the importance of regular eye care for older drivers.

## 13.4 Visual and Other Factors Which Are Predictive of Driving Performance and Crash Risk

On-road assessment, simulator studies, naturalistic driving, and studies of crash risk have all been used to assess the impact of deficits in vision on driving performance and crash risk (Table 13.1). Among the factors identified in these studies are poor contrast sensitivity, visual field loss, and glare sensitivity (Dawson et al. 2010; Ball et al. 1993; Rubin et al. 2007).

Early research focused on measuring the effect of reduced visual acuity on crash risk. A study involving more than 13,000 drivers, published in 1976, found a correlation between increased crash risk and decreased acuity (Hofstetter 1976). Gresset and Meyer (1994) found that crash rates were only increased when reduced visual acuity was associated with compromised binocular vision (Gresset and Meyer 1994). Data pertaining to crash rates and decreased visual acuity remain equivocal, and this may be a function of the fact that most persons who drive do not have significant deficits in high-contrast acuity.

Contrast sensitivity appears to be a better predictor of driving performance than high-contrast visual acuity. Owsley et al. (2001) showed that contrast sensitivity was associated with crash involvement where visual acuity and glare sensitivity showed no significant associations. The most common cause of reduced contrast sensitivity is cataract which causes predictable changes to vision. A literature review examining impact of unoperated cataract by Conner-Spady et al. (2007) reported an increased risk of motor vehicle crashes. Older drivers with cataract have been found to be 2.5 times more likely to have a history of crash involvement, over a period of 5 years, than those of the same age without cataract, even after adjustments for age, general physical and mental health, and driving exposure (Owsley et al. 1999). Owsley et al. (2002) also demonstrated the benefit of cataract surgery in decreasing crash risk in a longitudinal dataset. Patients who elected to have cataract surgery had approximately half the rate of subsequent crash involvement compared to those that declined surgery during the 4-year follow-up. Additionally, when compared to the crash rates during the years prior to the study, the nonsurgical group had a significant (72 %) increase in crash rate during the follow-up period, while the surgical group demonstrated a statistically nonsignificant increase of 27 %.

In a Swedish study (Monestam et al. 2005), 50 % of cataract patients reported visual difficulties with daytime driving. After surgery, this figure decreased to 6 %. Before surgery, 69 % reported difficulties with driving in darkness. After surgery, only 24 % of patients had difficulties. Similarly, Elliot et al. (2000) reported that after bilateral cataract surgery, the perceived ability to drive at night as recorded by the Activities of Daily Vision Scale (ADVS) returned to age-matched norms. Another study by Wood and Carberry (2006) showed that objectively analyzed driving performance also improved following cataract surgery on a closed-road circuit.

These findings with relation to cataract vision impairment are important as a large and increasing number of older drivers will require cataract surgery during the later stages of their driving career. These numbers will likely increase based on trends in aging of the population (Statistics Portal 2007), the increasing numbers of older people who drive (National Highway Traffic Safety 2009), and prevalence of cataract in older age groups. A prospective multicenter survey of European drivers ($n = 2{,}211$) (Nischler et al. 2010) found approximately 1 in 5 drivers aged 75 years and older had moderate to severe bilateral cataract. This study also found that the prevalence of cataract in the older driving population varied between jurisdictions, most likely due to differences in mandatory vision tests with license renewal or efficiency of surgical services.

Bohensky et al. (2008) reviewed the evidence for a relationship between visual field loss and driving performance or crash risk, referred to earlier meta-analyses and reviewed recent evidence from 2004 to 2007. The data are somewhat equivocal, most likely due to differences in methodology, and the strongest evidence comes from the Salisbury Eye Evaluation Study, a large population-based study (Rubin et al. 2007) which found field loss to be predictive of crash involvement (Table 13.1). Loss in the inferior peripheral visual field was the most relevant to crash risk. This study also found that glare sensitivity and worse scores on a test of the useful field of view (UFOV) were predictive of crash involvement. A 40 % loss of the UFOV resulted in a two times increased crash risk. Loss of three letters of acuity in glare conditions was found to increase crash risk by approximately two times, and this type of loss

may be encountered in cataract which can cause symptoms of glare.

The findings relating to vision – contrast sensitivity, cataract, and visual field loss – are not surprising considering that drivers are strongly dependent on vision for navigation and operation of a motor vehicle. However, in older populations, measures of cognition such as visual attention are also predictive of driving performance. Loss of cognition is reflected in the type of crashes involving older drivers which are more likely to be at intersections and in complex driving situations where attention and rapid reactions would be critical to safe navigation (Ryan et al. 1998; Braitman et al. 2007). The combined importance of vision and cognition has been shown in several research studies (Wood et al. 2009b; Cantin et al. 2009), and in one study of older drivers using a Driving Monitor System, errors in making lane changes were associated entirely with measures of cognitive loss (Munro et al. 2010). There are specific tests of various cognitive domains which have been associated with driving performance or crash risk (Table 13.1). The Trail Making Test Part A is a test of visual scanning and processing, whereas Part B is a test of executive function but requires visual scanning and search (Bowie and Harvey 2006). The test is paper-based and portable and proposed as a useful stand-alone test (Betz and Fisher 2009) or part of a screening and evaluation process (Staplin et al. 2003; Park et al. 2011) for evaluating fitness to drive. Longer times to complete the TMT Part B have been associated with poor driving performance in a number of studies (Adrian et al. 2011; Richardson and Marottoli 2003; Freund and Colgrove 2008; Andrews and Westerman 2012).

Ball and collaborators have proposed the "Useful Field of View" (UFOV) as a measure of both visual and cognitive function that is predictive of crash involvement (Ball et al. 1993). They have created two version of the UFOV, one, a measure of the extent of attentional visual fields and the other, a fixed field in which processing speed is measured. In their statistical modeling, they demonstrated that central vision, peripheral vision, eye health, and mental status were predictive of the UFOV result, which in turn predicted crash risk. They found that older adults with a 40 % reduction in UFOV were approximately six times more likely to have been involved in crashes during the preceding 5 years (Ball et al. 1993). The predictive value of the UFOV has been demonstrated as an independent predictor of driving performance (Horswill et al. 2010) and crash risk (Rubin et al. 2007) and incorporated into a battery of tests designed to predict crash risk (Staplin et al. 2003). Hassan et al. (2008) measured the attentional visual field using a divided attention protocol out to 20° from fixation. A restricted vertical visual field was associated with failure to stop at red traffic lights (West et al. 2010), but to date, the attentional visual field test has not been evaluated with relation to crash risk.

While the results from the studies summarized in Table 13.1 may seem conflicting, much of the differences are due to study design and differences in the set of functional tests and other factors considered in the analyses. Some studies have focused on visual factors and visual attention (Rubin et al. 2007), while others have mostly tests of cognitive function (Staplin et al. 2003; Stutts et al. 1998; Park et al. 2011; Andrews and Westerman 2012; Shanmugaratnam et al. 2010) or included simple measures of vision such as self-report of eye disease (O'Connor et al. 2010) or visual acuity alone (Richardson and Marottoli 2003). There are a small number of studies of driving performance or crash risk which have a comprehensive range of both vision and cognitive function testing (Dawson et al. 2010; Keay et al. 2009a; Munro et al. 2010; West et al. 2010).

## 13.5 Assessing Fitness to Drive in Older Populations

Mathias and Lucas reviewed cognitive tests which can predict driving performance and found that a variety of tests appear suitable (Mathias and Lucas 2009). Choice of an appropriate test will therefore depend on the practical considerations like portability and ease of use. Similar considerations apply for assessing driving. While on-road testing is a gold standard for evaluating fitness to drive, it is resource intensive.

An off-road hazard perception suitable for use outside the laboratory has been developed called the Hazard Perception Test (Horswill et al. 2008). After a preliminary video sequence used to familiarize with the test, the participants watch traffic sequences and indicate every time a traffic conflict occurs. Response times have been measured to be longer with increasing age, and increased latency in hazard perception was related to crash risk (Horswill et al. 2010). Break reaction time is another off-road test, similarly related to declines visual and cognitive function (Horswill et al. 2008; Martin et al. 2010; Zhang et al. 2007).

Though there is considerable evidence for functional deficits precipitating poor driving performance or crash risk, proving the effectiveness of screening tests to determine fitness to drive has been fraught with controversy. A recent Cochrane review of vision screening tests, with the objective of examining the evidence for crash and injury prevention, found no evidence to support their use (Subzwari et al. 2009). Review of a series of screening protocols concluded that none of the tests were cost-effective in identifying drivers at risk of crash (Viamonte et al. 2006). Others have speculated that screening tests can never be cost-effective (Bedard et al. 2008) and that on-road tests are more effective in identifying at-risk drivers (Dobbs 2008). While the strongest evidence to date are for perceptual/cognitive tests with relation to crash risk (Table 13.1), their practical application may be best as an aid to planning the transition to not driving rather than a pass/fail screening tool (Langford 2008; Langford et al. 2008).

## 13.6 Self-Regulation of Driving in Older Populations

While there are visual requirements and medical conditions which preclude driving in many jurisdictions, self-regulation by older drivers is another strategy to modulate their safety. Approximately 3–5 % (Foley et al. 2002; Freeman et al. 2005) of older drivers cease driving each year, but a larger proportion of drivers restrict the way they drive in some capacity. Population-based surveys find that one-quarter to one-third of older drivers have made at least one adaptation to the way they drive (Charlton et al. 2006; Gallo et al. 1999; Molnar and Eby 2008). A national survey of a representative sample of older drivers in the USA aged 50 years and older found that in practice, self-regulation is a product of personal circumstances, vehicle features and alternative transport, individual preferences, and confidence in driving ability (Donorfio et al. 2009). This explanation is supported by findings from epidemiologic studies (Tables 13.2 and 13.3) where gender differences exist and personality factors appear to play a role in driving behavior. Most studies examining self-regulation conclude that women are more likely to regulate their driving than men (Kostyniuk and Molnar 2008; Brabyn et al. 2005) and that men were more likely than women to be drivers with similar levels of disability (Ross et al. 2009). Personal preferences (Keay et al. 2009b), depressive symptoms (Keay et al. 2009b; Brabyn 2005), and social situation (housing, widowed/divorced, employment status) (Braitman and Williams 2011) also have a role in self-regulation.

Self-regulation has been documented in relation to health conditions and cognitive, sensory, and motor functioning (Tables 13.2 and 13.3). Self-regulation may explain the paradoxical relationship noted where lower crash risk is found in those with some increased glare sensitivity and visual field loss (within a subgroup with moderate to better vision) (Rubin et al. 2007). Molnar and Eby reported that drivers who avoided driving at night had worse performance in an on-road assessment (Molnar and Eby 2008), and this further supports that poor drivers restrict their driving exposure.

Longitudinal studies and large cross-sectional studies documenting the link between functional status and driving cessation or self-regulation of driving are summarized in Tables 13.2 and 13.3, respectively. Several studies have pointed to decline in cognitive function being the main predictor of driving cessation (Anstey et al. 2006; Edwards et al. 2008a; Ackerman et al. 2008) though visual function is also predictive, specifically poor contrast sensitivity and visual field loss (Freeman et al. 2005). Others have suggested that while regulation of driving exposure is strongly related to function, cessation is more

**Table 13.2** Studies evaluating driving cessation

| Study | Sample | Age mean (range) | Study findings |
|---|---|---|---|
| *Longitudinal studies* | | | |
| Marottoli et al. (1993) | $n=589$ | 65+ | Older age and social factors such as not working and low income, neurologic disease, cataract, and increasing disability were predictive of driving cessation after 5 years |
| Freeman et al. (2005) | $n=1,824$ | 73 (65–84) | Poor CS and central and peripheral visual field loss were predictive of driving cessation after 8 years. Glare sensitivity was not predictive |
| Anstey et al. (2006) | $n=753$ | (70+) | Self-related health and cognitive function were more important than medical conditions or sensory function for predicting driving cessation after 5 years |
| Edwards et al. (2008a) | $n=1,656$ | 73 (65–91) | Slower speed of processing (Digit Symbol Substitution and UFOV) was predictive of driving cessation after 5 years after adjusting for baseline driving. Visual acuity and diagnosis of eye disease not predictive |
| Ackerman et al. (2008) | $n=1,838$ | 73 (65+) | Older age, poorer balance, slower cognitive speed of processing (UFOV), and poor instrumental functional performance were predictive of driving cessation at 3 years |
| Edwards et al. (2010) | $n=1,248$ | 70 (55–96) | Among a comprehensive battery of cognitive tests, older age and slower speed of processing (UFOV) were predictive of driving cessation at 10 years |
| *Large cross-sectional studies* | | | |
| Freund and Szinovacz (2002) | $n=5,141$ | 77 (70+) | Not being a current driver is related to poor function (cognition, vision, limitations on ADL) but also social circumstances such as having an alternative driver |
| Siren et al. (2004) | $n=4,970$ | All aged 70 | People who gave up driving at age 70 had poor overall health and general well-being rather than conditions particularly relevant to driving ability |
| Ross et al. (2009) | $n=5,206$ | (65–103) | Men more likely to drive with higher levels of disability. Vision impairment, more medical conditions, and older age predictive of not driving. Higher-level occupation and married status increased likelihood of being a driver |

*HC* high contrast, *LC* low contrast, *VA* visual acuity, *CS* contrast sensitivity, *AVF* attentional visual field, *MMSE* mini-mental state examination, *SF-36* short form-36, *TMT* trail making test, *ADL* activities of daily living

likely a product of personal circumstances like no longer being employed, having a low income (Marottoli et al. 1993), and poor general health and disability (Anstey et al. 2006; Marottoli et al. 1993; Siren et al. 2004). Availability of a spouse or relative who drives is also of practical significance and enables some older drivers to give up driving knowing they have alternatives (Freund and Szinovacz 2002).

In contrast self-regulation is closely related to functional status, and Freeman showed that types of restrictions such as reduced mileage and not driving at night were driven by different types of visual deficits (Freeman et al. 2006b). Inclusion of a comprehensive battery of visual and cognitive tests in the Salisbury Eye Evaluation Driving Study found that both vision (poor contrast sensitivity) and cognition were related to self-regulation of driving (Keay et al. 2009b). The ability to self-regulate appropriately requires that the driver is aware of functional limitations. This has been explored by several authors who find supporting data that there is often a gap between test performance and awareness of limitations (Horswill et al. 2011; Kay et al. 2009).

Self-administered computer tools have been proposed to evaluate fitness to drive and encourage self-regulation (Edwards et al. 2008b; Molnar et al. 2010). These are new initiatives and

**Table 13.3** Studies which have evaluated driver characteristics which predict self-regulation of driving behavior

| Study | Sample | Age mean (range) | Outcome | Study findings |
|---|---|---|---|---|
| *Longitudinal studies* | | | | |
| Marottoli et al. (1993) | $n=589$ | 65+ | Low vs. high mileage at 5 years | Increasing age and disability were predictive of low mileage. Women, older-aged drivers, those who are not working, drivers with low income, and individuals with increasing social activities were likely to be driving but at low mileage |
| Freeman et al. (2006b) | $n=1,605$ | (65–84) | Restricted mileage, avoiding night driving, or in unfamiliar areas at 2 years post assessment | Among a comprehensive battery of vision tests, differing aspects of vision accounted for types of restrictions: mileage (VA, CS, central and peripheral VF), night driving (CS, central and peripheral VF), or unfamiliar places (VA) |
| Keay et al. (2009b) | $n=1,237$ | 75 (67–87) | Ceasing or restricting driving to local neighborhood | Within a comprehensive battery of tests of vision and cognition, poor CS, slow time for TMT Part A, poor visuo-motor integration (VMI), and preference to not drive. Females were also more likely to cease or restrict driving. Depressive symptoms and driving preferences were also predictive |
| Braitman and Williams (2011) | $n=2,650$ ($n=1,437$ all 4 surveys) | 74 (65+) | Number of driving situations avoided or restricting driving to low mileage | This study considered self-reported difficulty with distance, near and peripheral vision, physical mobility impairment, and medical conditions, but these were not predictive. Memory and mobility impairment were predictive of avoiding driving situations. Reduced mileage was associated with personal and social situation (widowed or divorced, moved, retired, or lost job) |
| *Large cross-sectional studies* | | | | |
| Brabyn et al. (2005) | $n=752$ | 73 (58–96) | Not driving at night | Analyzed data separately for men and women as factors differed and women more likely to change driving habits. Predictive factors in men: CS, age, depression, medical conditions, and cognition; in women: LCVA in glare, age, depression, medical conditions, and cognition |
| Freund and Szinovacz (2002) | $n=5,141$ | 77 (70+) | Drives short distances only | Poor performance on an aggregate index of cognitive poor self-rated vision, limitations on ADL were predictive of only driving short distances |
| Kostyniuk and Molnar (2008) | $n=961$ | 74 (65+) | Regulatory driving practices in driving scenarios (in rain etc.) | Worse mobility and poor vision increased likelihood of self-regulation. Women more likely to self-regulate than older drivers |

*HC* high contrast, *LC* low contrast, *VA* visual acuity, *CS* contrast sensitivity, *AVF* attentional visual field

their effectiveness in preventing crashes is not proven (Bedard et al. 2011; Porter and Tuokko 2011). It remains that while self-restriction is a promising tool to promote safety, external factors may override considerations of driving ability and prevent an informed and timely decision (Classen et al. 2007). The availability of alternate transportation is an important consideration for policy makers interested in promoting safe mobility (Charlton et al. 2006). Substantial educational resources are required to not only improve awareness of functional limitations but to help plan for alternatives to driving.

## Conclusions

Visual function is an important component of fitness to drive; however, measures which include cognitive function in addition to vision strengthen the ability to predict crash risk. A number of studies have shown evidence of cautious driving in the presence of visual and cognitive functional decline, though the safety benefits of self-regulation remain to be firmly established. Safety benefits have been demonstrated for cataract surgery (Meuleners et al. 2012; Owsley et al. 2002), and novel approaches such as cognitive training have shown promise (Ball et al. 2010). It remains that the transition to not driving requires planning and constitutes a major life change. Collaboration between older drivers, their health care providers, family, and support networks can optimize this process.

**Acknowledgments** Conflict of interest: none; Ethical standards; Informed consent – not applicable; Animal rights – not applicable.

## References

Ackerman ML et al (2008) Examination of cognitive and instrumental functional performance as indicators for driving cessation risk across 3 years. Gerontologist 48(6):802–810

Adrian J et al (2011) Personality traits and executive functions related to on-road driving performance among older drivers. Accid Anal Prev 43(5):1652–1659

Andrews EC, Westerman SJ (2012) Age differences in simulated driving performance: compensatory processes. Accid Anal Prev 45(2):660–668

Anstey KJ et al (2006) Predicting driving cessation over 5 years in older adults: psychological well-being and cognitive competence are stronger predictors than physical health. J Am Geriatr Soc 54(1):121–126

Antin J (2010) Older driver naturalistic driving study. Blacksburg, Virginia: Virginia Tech Transportation Institute

Australian Bureau of Statistics (2008) Population aging in New South Wales. Australian Bureau of Statistics, Canberra

Baldwin KC, Duncan DD, West SK (2004) The driver monitor system: a means of assessing driver performance. Johns Hopkins APL Tech Dig 25:269–277

Ball K et al (1993) Visual attention problems as a predictor of vehicle crashes in older drivers. Invest Ophthalmol Vis Sci 34(11):3110–3123

Ball K et al (2010) Cognitive training decreases motor vehicle collision involvement of older drivers. J Am Geriatr Soc 58(11):2107–2113

Bedard M et al (2008) Predicting driving performance in older adults: we are not there yet! Traffic Inj Prev 9(4):336–341

Bedard M et al (2011) Roadwise review has limited congruence with actual driving performance of aging drivers. Accid Anal Prev 43(6):2209–2214

Betz ME, Fisher J (2009) The Trail-making Test B and driver screening in the emergency department. Traffic Inj Prev 10(5):415–420

Blanchard RA, Myers AM (2010) Examination of driving comfort and self-regulatory practices in older adults using in-vehicle devices to assess natural driving patterns. Accid Anal Prev 42(4):1213–1219

Bohensky M et al (2008) Implications of vision testing for older driver licensing. Traffic Inj Prev 9(4): 304–313

Bowers A et al (2005) On-road driving with moderate visual field loss. Optom Vis Sci 82(8): 657–667

Bowie CR, Harvey PD (2006) Administration and interpretation of the Trail Making Test. Nat Protoc 1(5):2277–2281

Brabyn L (2005) Solutions for characterising natural landscapes in New Zealand using geographical information systems. J Environ Manage 76(1):23–34

Brabyn JA et al (2005) Night driving self-restriction: vision function and gender differences. Optom Vis Sci 82(8):755–764

Braitman KA, Williams AF (2011) Changes in self-regulatory driving among older drivers over time. Traffic Inj Prev 12(6):568–575

Braitman KA et al (2007) Factors leading to older drivers' intersection crashes. Traffic Inj Prev 8(3):267–274

Cantin V et al (2009) Mental workload when driving in a simulator: effects of age and driving complexity. Accid Anal Prev 41(4):763–771

Cerrelli EC (2007) Crash data and rates for Age-Sex Groups of drivers, 1996. Available from http://www.nhtsa.dot.gov/people/ncsa/. Accessed on January 2012

Charlton J et al (2006) Self-regulatory driving practices of older drivers in the Australian Capital Territories and New South Wales. Monash University Accident Research Center, Clayton

Classen S et al (2007) Population-based health promotion perspective for older driver safety: conceptual framework to intervention plan. Clin Interv Aging 2(4):677–693

Conner-Spady B et al (2007) A systematic literature review of the evidence on benchmarks for cataract surgery waiting time. Can J Ophthalmol 42(4):543–551

Dawson JD et al (2010) Neuropsychological predictors of driving errors in older adults. J Am Geriatr Soc 58(6): 1090–1096

Department of the Environment Transport and the Regions United Kingdom (2000) Older (60+) car drivers in road accidents, Great Britain, 1998. DETR, London

Dickerson AE et al (2007) Transportation and aging: a research agenda for advancing safe mobility. Gerontologist 47(5):578–590

Dingus TA et al (2006) The 100-car naturalistic driving study, phase II – results of the 100-car field experiment. National Highway Transport Safety Administration, Virginia

Dobbs BM (2008) Aging baby boomers – a blessing or challenge for driver licensing authorities. Traffic Inj Prev 9(4):379–386

Donorfio LK et al (2009) To drive or not to drive, that isn't the question-the meaning of self-regulation among older drivers. J Safety Res 40(3):221–226

Edwards JD et al (2008a) Longitudinal predictors of driving cessation among older adults from the ACTIVE clinical trial. J Gerontol B Psychol Sci Soc Sci 63(1): 6–12

Edwards JD et al (2008b) Acceptability and validity of older driver screening with the DrivingHealth Inventory. Accid Anal Prev 40(3):1157–1163

Edwards JD et al (2010) Ten years down the road: predictors of driving cessation. Gerontologist 50: 393–399

Elliott DB et al (2000) Improvements in clinical and functional vision and quality of life after second eye cataract surgery. Optom Vis Sci 77(1):13–24

Foley DJ et al (2002) Driving life expectancy of persons aged 70 years and older in the United States. Am J Public Health 92(8):1284–1289

Freeman EE et al (2005) Measures of visual function and time to driving cessation in older adults. Optom Vis Sci 82(8):765–773

Freeman EE et al (2006a) Driving status and risk of entry into long-term care in older adults. Am J Public Health 96(7):1254–1259

Freeman EE et al (2006b) Measures of visual function and their association with driving modification in older adults. Invest Ophthalmol Vis Sci 47(2): 514–520

Freund B, Colgrove LA (2008) Error specific restrictions for older drivers: promoting continued independence and public safety. Accid Anal Prev 40(1): 97–103

Freund B, Szinovacz M (2002) Effects of cognition on driving involvement among the oldest old: variations by gender and alternative transportation opportunities. Gerontologist 42(5):621–633

Gallo JJ, Rebok GW, Lesikar SE (1999) The driving habits of adults aged 60 years and older. J Am Geriatr Soc 47(3):335–341

Grabowski DC, Campbell CM, Morrisey MA (2004) Elderly licensure laws and motor vehicle fatalities. JAMA 291(23):2840–2846

Gresset JA, Meyer FM (1994) Risk of accidents among elderly car drivers with visual acuity equal to 6/12 or 6/15 and lack of binocular vision. Ophthalmic Physiol Opt 14(1):33–37

Gstalter H, Fastenmeier W (2010) Reliability of drivers in urban intersections. Accid Anal Prev 42(1): 225–234

Hanrahan RB et al (2009) The association of driver age with traffic injury severity in Wisconsin. Traffic Inj Prev 10(4):361–367

Hassan SE et al (2008) Cognitive and vision loss affects the topography of the attentional visual field. Invest Ophthalmol Vis Sci 49:4672–4678

Hofstetter HW (1976) Visual acuity and highway accidents. J Am Optom Assoc 47(7):887–893

Horswill MS et al (2008) The hazard perception ability of older drivers. J Gerontol B Psychol Sci Soc Sci 63(4):P212–P218

Horswill MS et al (2010) The crash involvement of older drivers is associated with their hazard perception latencies. J Int Neuropsychol Soc 16(5):939–944

Horswill MS et al (2011) Older drivers' insight into their hazard perception ability. Accid Anal Prev 3(6): 2121–2127

Kay LG, Bundy AC, Clemson L (2009) Awareness of driving ability in senior drivers with neurological conditions. Am J Occup Ther 63(2):146–150

Keay L et al (2009a) Urban and rural differences in older drivers' failure to stop at stop signs. Accid Anal Prev 41(5):995–1000

Keay L et al (2009b) Visual and cognitive deficits predict stopping or restricting driving: the Salisbury Eye Evaluation Driving Study (SEEDS). Invest Ophthalmol Vis Sci 50(1):107–113

Keeffe JE et al (2002) Vision impairment and older drivers: who's driving? Br J Ophthalmol 86(10):1118–1121

Kostyniuk LP, Molnar LJ (2008) Self-regulatory driving practices among older adults: health, age and sex effects. Accid Anal Prev 40(4):1576–1580

Kostyniuk LP, Shope JT (2003) Driving and alternatives: older drivers in Michigan. J Safety Res 34(4): 407–414

Langford J (2008) Usefulness of off-road screening tests to licensing authorities when assessing older driver fitness to drive. Traffic Inj Prev 9(4):328–335

Langford J, Methorst R, Hakamies-Blomqvist L (2006) Older drivers do not have a high crash risk – a replication of low mileage bias. Accid Anal Prev 38(3): 574–578

Langford J et al (2008) TRB Workshop 2007: Licensing authorities' options for managing older driver safety – practical advice from the researchers. Traffic Inj Prev 9(4):278–281

Lee HC, Cameron D, Lee AH (2003) Assessing the driving performance of older adult drivers: on-road versus simulated driving. Accid Anal Prev 35(5): 797–803

Li G, Braver ER, Chen LH (2003) Fragility versus excessive crash involvement as determinants of high death rates per vehicle-mile of travel among older drivers. Accid Anal Prev 35(2):227–235

Lyman S et al (2002) Older driver involvements in police reported crashes and fatal crashes: trends and projections. Inj Prev 8(2):116–120

Marottoli RA et al (1993) Driving cessation and changes in mileage driven among elderly individuals. J Gerontol 48(5):S255–S260

Marottoli RA et al (2000) Consequences of driving cessation: decreased out-of-home activity levels. J Gerontol B Psychol Sci Soc Sci 55(6):S334–S340
Marshall SC et al (2007) Measurement of driving patterns of older adults using data logging devices with and without global positioning system capability. Traffic Inj Prev 8(3):260–266
Martin PL et al (2010) Comparison between younger and older drivers of the effect of obstacle direction on the minimum obstacle distance to brake and avoid a motor vehicle accident. Accid Anal Prev 42(4):1144–1150
Mathias JL, Lucas LK (2009) Cognitive predictors of unsafe driving in older drivers: a meta-analysis. Int Psychogeriatr 21(4):637–653
McGwin G Jr, Owsley C, Ball K (1998) Identifying crash involvement among older drivers: agreement between self-report and state records. Accid Anal Prev 30(6): 781–791
McLaughlin SB, Hankey JM, Dingus TA (2008) A method for evaluating collision avoidance systems using naturalistic driving data. Accid Anal Prev 40(1): 8–16
Meuleners LB et al (2006) Fragility and crash over-representation among older drivers in Western Australia. Accid Anal Prev 38(5):1006–1010
Meuleners LB et al (2012) The effectiveness of cataract surgery in reducing motor vehicle crashes: a whole population study using linked data. Ophthalmic Epidemiol 19:23–28
Molnar LJ, Eby DW (2008) The relationship between self-regulation and driving-related abilities in older drivers: an exploratory study. Traffic Inj Prev 9(4):314–319
Molnar LJ et al (2010) Increasing self-awareness among older drivers: the role of self-screening. J Safety Res 41(4):367–373
Monestam E, Lundquist B, Wachtmeister L (2005) Visual function and car driving: longitudinal results 5 years after cataract surgery in a population. Br J Ophthalmol 89(4):459–463
Munro CA et al (2010) Predictors of lane change errors among elderly drivers. J Am Geriatr Soc 58:457–464
National Highway Traffic Safety Administration (2009) Traffic safety facts 2009 data: older population. National Center for Statistics and Analysis, Washington, D.C.
Niele VL et al (2009) An overview of the 100-car naturalistic study and findings. National HIghway Traffic Safety Administration, Washington, D.C.
Nischler C et al (2010) Cataract and pseudophakia in elderly European drivers. Eur J Ophthalmol 20:892–901
O'Connor MG et al (2010) The 4Cs (crash history, family concerns, clinical condition, and cognitive functions): a screening tool for the evaluation of the at-risk driver. J Am Geriatr Soc 58(6):1104–1108
OECD Statistics Portal (2007) OECD population pyramids in 2000 and 2050. Available from http://www.oecd.org/. Accessed on January 2012
Owsley C et al (1999) Older drivers and cataract: driving habits and crash risk. J Gerontol A Biol Sci Med Sci 54(4):M203–M211
Owsley C et al (2001) Visual risk factors for crash involvement in older drivers with cataract. Arch Ophthalmol 119(6):881–887
Owsley C et al (2002) Impact of cataract surgery on motor vehicle crash involvement by older adults. JAMA 288(7):841–849
Park SW et al (2011) Association between unsafe driving performance and cognitive-perceptual dysfunction in older drivers. PM R 3(3):198–203
Porter MM, Tuokko HA (2011) An evaluation of the road-wise review: a mixed methods approach. Traffic Inj Prev 12(5):451–458
Porter MM, Whitton MJ (2002) Assessment of driving with the global positioning system and video technology in young, middle-aged, and older drivers. J Gerontol A Biol Sci Med Sci 57(9): M578–M582
Pradhan AK et al (2005) Using eye movements to evaluate effects of driver age on risk perception in a driving simulator. Hum Factors 47(4):840–852
Richardson ED, Marottoli RA (2003) Visual attention and driving behaviors among community-living older persons. J Gerontol A Biol Sci Med Sci 58(9): M832–M836
Ross LA et al (2009) Older drivers in Australia: trends in driving status and cognitive and visual impairment. J Am Geriatr Soc 57:1868–1873
Rubin GS et al (2007) A prospective, population-based study of the role of visual impairment in motor vehicle crashes among older drivers: the SEE study. Invest Ophthalmol Vis Sci 48(4):1483–1491
Ryan GA, Legge M, Rosman D (1998) Age related changes in drivers' crash risk and crash type. Accid Anal Prev 30(3):379–387
Shanmugaratnam S, Kass SJ, Arruda JE (2010) Age differences in cognitive and psychomotor abilities and simulated driving. Accid Anal Prev 42(3): 802–808
Shechtman O et al (2009) Comparison of driving errors between on-the-road and simulated driving assessment: a validation study. Traffic Inj Prev 10(4):379–385
Siren A, Hakamies-Blomqvist L, Lindeman M (2004) Driving cessation and health in older women. J Appl Gerontol 23(1):58–69
Staplin L, Gish KW, Wagner EK (2003) MaryPODS revisited: updated crash analysis and implications for screening program implementation. J Safety Res 34(4):389–397
Stutts JC, Stewart JR, Martell C (1998) Cognitive test performance and crash risk in an older driver population. Accid Anal Prev 30(3):337–346
Subzwari S et al (2009) Vision screening of older drivers for preventing road traffic injuries and fatalities. Cochrane Database Syst Rev (1):CD006252
Viamonte SM, Ball KK, Kilgore M (2006) A cost-benefit analysis of risk-reduction strategies targeted at older drivers. Traffic Inj Prev 7(4):352–359
West SK et al (2010) Older drivers and failure to stop at red lights. J Gerontol A Biol Sci Med Sci 65: 179–183

Williams AF, Shabanova VI (2003) Responsibility of drivers, by age and gender, for motor-vehicle crash deaths. J Safety Res 34(5):527–531

Wood JM (2002) Age and visual impairment decrease driving performance as measured on a closed-road circuit. Hum Factors 44(3):482–494

Wood JM, Carberry TP (2006) Bilateral cataract surgery and driving performance. Br J Ophthalmol 90(10): 1277–1280

Wood JM et al (2009a) The on-road difficulties of older drivers and their relationship with self-reported motor vehicle crashes. J Am Geriatr Soc 57:2062–2069

Wood J, Chaparro A, Hickson L (2009b) Interaction between visual status, driver age and distracters on daytime driving performance. Vision Res 49: 2225–2231

Zhang J et al (2000) Factors affecting the severity of motor vehicle traffic crashes involving elderly drivers in Ontario. Accid Anal Prev 32(1):117–125

Zhang L et al (2007) Visual and cognitive predictors of performance on brake reaction test: Salisbury eye evaluation driving study. Ophthalmic Epidemiol 14(4):216–222

# Depressive and Cognitive Disorders in Patients with AMD

14

Robin J. Casten and Barry W. Rovner

## 14.1 Introduction

Depression and cognitive impairment are two common psychiatric disorders in patients with age-related macular degeneration (AMD). Depression is fairly prevalent in AMD, and research that has studied its effects on quality of life and daily functioning are presented in this chapter. Methods for detecting depression are suggested. This is followed by a review of research that has tested the efficacy of various behavioral interventions to treat or prevent depression in AMD, as well as a discussion on the impact of rehabilitation on depression. This chapter also reviews research that has documented relationships between AMD and cognitive impairment. Theories that explain the mechanisms responsible for the co-occurrence of these two conditions are discussed.

R.J. Casten, PhD (✉)
Department of Psychiatry and Human Behavior,
Jefferson Medical College,
Jefferson Hospital for Neuroscience,
900 Walnut Street, 2nd Floor,
Philadelphia, PA 19107, USA
e-mail: robin.casten@jefferson.edu

B.W. Rovner, MD
Departments of Psychiatry and Neurology,
Jefferson Medical College,
Jefferson Hospital for Neuroscience,
900 Walnut Street, 2nd Floor,
Philadelphia, PA 19107, USA
e-mail: barry.rovner@jefferson.edu

## 14.2 Depression in Age-Related Macular Degeneration

Depression in older adults is a serious yet often underdiagnosed and undertreated medical condition. Current research estimates the prevalence of depression among community-dwelling older people to be approximately 12 % (for both major and minor depression combined) (Steffens et al. 2009). Common risk factors for late life depression include female sex (Byers et al. 2010), recent bereavement, physical disability, medical comorbidity, sleep disturbance, and previous depression (Cole 2005). Vision impairment also confers a high risk for depression, with odds ratios averaging around 1.9 (Nyman et al. 2009). The prevalence of depression among older persons with impaired vision ranges from about 14–63 % (Brody 2001; Evans et al. 2007; Jones et al. 2009; Rovner and Ganguli 1998).

A diagnosis of major depressive disorder is based on a specific set of criteria whereby sad mood or an inability to experience pleasure (anhedonia), in addition to at least four other symptoms (e.g., sleep or appetite disturbance, trouble concentrating, feelings of guilt, hopelessness), are present for at least 2 weeks (American Psychiatric Association 2000). Subthreshold depression is a syndrome whereby a patient has at least 1 but fewer than 4 depressive symptoms. Both types of depression are common in older adults with impaired vision. In fact, subthreshold depression in visually impaired people is a strong risk factor for a future depressive episode (Rovner 2001, unpublished raw data).

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_14, 

Most cases of late-onset vision loss in the US are attributable to age-related macular degeneration (AMD), with almost ten million people being affected (Congdon et al. 2004). The effect of AMD on a patient's life can be devastating. In a study of 86 AMD patients, overall ratings of quality of life were substantially lower than that of visually intact older people, older people with severe chronic obstructive pulmonary disease, and patients with AIDS (Williams et al. 1998). Compared to nonvisually impaired older people, patients with AMD were 8 times more likely to have trouble shopping, 13 times more likely to have difficulty managing finances, 4 times more likely to have problems with meal preparation, 9 times more likely to report difficulty with light housework, and 12 times more likely to have trouble using a telephone. AMD is also a risk factor for falls and subsequent hip fracture (Crews and Campbell 2004).

Given the disabling effects of AMD, it is not surprising that there is a high rate of depression in this population (most estimates hover around 30 %) (Brody et al. 2001; Hayman et al. 2007; Horowitz et al. 2005a; Rovner et al. 2002). These high rates are alarming due to the serious health consequences related to untreated depression in people with vision loss. A population-based study showed that comorbid vision impairment and depression in older people is associated with smoking, obesity, physical inactivity, and worse self-rated health (Jones et al. 2009). Vision impairment in older people is also a risk factor for suicide (Lam et al. 2008).

Depression can amplify the disabling effects of AMD. Depressed individuals with vision loss experience worse function and disability compared to their nondepressed counterparts (Jones et al. 2009). This effect is upheld even when controlling for severity of vision impairment (Rovner and Casten 2001), and it has been replicated in at least two other studies. Brody et al. (2001) found that depressed patients with impaired vision reported greater disability than nondepressed patients. In Rovner and Ganguli's (1998) study of 872 older adults, having combined vision impairment and depressive symptoms significantly increased the odds of functional impairment (Rovner and Ganguli 1998).

It is worth noting that subthreshold depression also has a profound effect on functioning. Horowitz et al. (2005b) compared functional disability ratings among three groups of older patients presenting for low-vision rehabilitation services: (1) those with major depression, (2) those with subthreshold depression, and (3) those with no depression. Those with subthreshold depression had levels of disability comparable to those with major depression; both depressed groups had significantly greater disability compared to subjects with no depression. Similar findings were observed by Rovner et al. (2006) who examined the relationships between disability and subthreshold depressive symptoms in 206 nondepressed AMD patients. Those with subthreshold depression had significantly worse vision function than those with no depression despite similar visual acuities. This rather robust finding was evident for both self-reported vision function and function ratings based on observation of task performance (e.g., check writing, pouring liquid).

There are several potential explanations for the high rate of depression in AMD. Functional losses due to vision impairment can erode one's sense of personal control and lead to feelings of inadequacy and helplessness. Social isolation can arise from mobility restrictions (e.g., difficulty driving, limited walking due to fear of falling), embarrassment about vision loss, and impairments in processing visual stimuli (e.g., reading nonverbal facial cues). Moreover, vision impairment can lead to a diminution or cessation of activities and pastimes that give life meaning and richness. Other factors that may increase the risk for depression in patients with impaired vision include negative life events (Rees et al. 2010) and dual sensory impairment (i.e., concurrent vision and hearing loss) (Crews and Campbell 2004).

Research shows that concomitant disability and activity disengagement are common mechanisms linking AMD to depression. The inability to partake in both discretionary activities (e.g., leisure, socializing) and activities that serve to maintain independence (e.g., driving, meal preparation) are associated with the development of depression. This was confirmed in a longitudinal

sample of patients with recent onset bilateral AMD which showed that AMD is depressogenic to the extent that patients relinquish activities that are personally important (Rovner et al. 2002). The relationship between difficulty caring out activities and depression is mediated by the severity of emotional distress caused by vision impairment (Rees et al. 2010).

Given the foregoing, helping people to maintain their independence, facilitating the acceptance of assistance when needed, and fostering an active lifestyle may be key to maintaining optimal psychological well being. Patients with AMD may suddenly find that habitual ways of carrying out everyday activities are no longer effective (this may be particularly so in the case of neovascular disease). These patients need guidance and support so that they can adapt effective coping strategies (i.e., learning new strategies for carrying out familiar, routine activities, learning to accept assistance from others, acquiring new activities to replace ones that are no longer possible). We discuss ahead that activity disengagement is also a risk factor for (or perhaps a prodromal symptom of) cognitive decline, and this too should be considered when fostering healthy adaptation to vision loss.

### 14.2.1 Preventing Depression in Age-Related Macular Degeneration

In view of the fact that depression (both major and subthreshold) can have such serious consequences for people with impaired vision, there is a need for guidelines on how to best to deal with depression as it relates to AMD. Depression in this context needs to be considered on two levels: prevention of future cases and treatment of acute episodes.

The first step in dealing with acute depression is to identify it. There are several quick and easy to administer depression screening instruments that can be used by nonmental health professionals. Three commonly used ones are the Geriatric Depression Scale (GDS) (Yesavage et al. 1983), the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977), and the Patient Health Questionnaire (PHQ) (Kroenke et al. 2001). Each of these instruments asks patients to rate the severity and/or frequency of depressive symptoms, and each yields quantitative scores that capture severity of depression. Each also has established cut points that indicate the possibility of major depression.

The most recent preferred practice guidelines from the American Academy of Ophthalmology (2008) recognize that depression is a common comorbid condition of AMD and that screening and providing appropriate referrals for depression are necessary when depression is suspected. However, depression screening should be considered for all AMD patients because relying on clinical judgment may not be the best strategy. Ophthalmologists often underestimate the negative effect of AMD on patients' quality of life, particularly among patients with better acuities (Brown and Brown 2010). Consequently, depression in older adults with vision loss is undertreated. For example, a recent study of 143 older persons with vision loss found that only 20 % of the depressed patients (12 of 60) were being treated for their depression (Rees et al. 2010). Moreover, research examining relationships between depression and severity of vision loss is mixed. Some studies show no relationship (Rovner et al. 2002; Rovner and Casten 2005), while others indicate that depression severity is worse in those with more substantial vision loss (Augustin et al. 2007). Until this uncertainty is resolved, it may be best to screen all AMD patients for possible depression, regardless of their acuity, disease stage, suspected presence of depressive symptoms, or AMD treatment received [20 % of patients undergoing anti-VEGF treatment remain depressed 3 months post treatment (Casten et al. 2010)].

Focusing efforts on the prevention of depression in AMD may be a cost-effective strategy because treating an active depressive episode is expensive, untreated depression may have significant health consensuses (heart disease, increased disability), and depression treatment is moderately efficacious at best (Gartlehner et al. 2007). Preventative interventions are catego-

rized at three levels: primary (goal is to decrease incidence), secondary (goal is to decrease prevalence), and tertiary (goal is relapse/recurrence prevention) (Mrazek and Haggerty 1994). Prevention efforts in AMD tend to focus on primary prevention, that is, strategies for averting the onset of a depressive episode. Primary prevention is conceptualized at three levels, depending on the target population. Universal interventions are aimed at the general population, for example, all patients who have AMD. Selected interventions target subgroups that have risk factors for depression (e.g., dual sensory loss), and indicated interventions are directed towards patients who are showing signs of the disease (i.e., subsyndromal depressive symptoms). A selected intervention approach is probably the most cost-effective strategy in AMD. Although the prevalence of depression is high (about 30 %), most patients with AMD will not become depressed.

An ideal target for prevention is patients with a recent decline in vision and subsequent new functional losses. The "Preventing Depression in AMD" trial (Rovner et al. 2007) tested the efficacy of a psychosocial intervention, problem-solving treatment (PST), to prevent depression in patients with new onset vision loss due to AMD. This standardized intervention was based on the premise that inaccurate appraisals of problems and dysfunctional problem-solving skills contribute to the onset of depression. Teaching patients effective problem-solving skills, therefore, may foster independence, preserve function, and prevent depressive symptoms. This study enrolled 206 nondepressed patients with bilateral neovascular AMD and recent vision loss. Subjects were randomized to either PST or a usual care control condition. The primary outcome was incidence of depressive disorders at 2 months (short-term effect); the trial also evaluated effects at 6 months (maintenance effect). A secondary goal was to determine whether PST could prevent the loss of participation in valued activities. PST-treated subjects had 6 in-home sessions in which a specially trained interventionist taught subjects in a systematic, step-by-step process for dealing with vision-related problems (e.g., trouble cooking, difficulty reading). Results indicated that PST successfully prevented depression at 2 months. About 12 % of the PST group became depressed compared to 23 % of the usual care group ($p < .05$). There was a parallel effect for function; 23 % of PST-treated subjects relinquished an important activity versus 37 % of usual care subjects. A meditational analysis determined that PST prevented depression to the extent that activity relinquishment was avoided. These effects, however, were not sustainable, as rates of depression were similar in both groups at 6 months (21 % of PST subjects developed depression vs. 27 % of control subjects).

This trial demonstrated that depression can be prevented in the short term; however, beneficial effects decay over time. Because neovascular AMD is characterized by episodes of sudden vision loss and corresponding functional declines, ongoing efforts to prevent depression may be needed throughout the course of the disease. This may involve monitoring and screening for events that may trigger depression and then administering maintenance or booster treatments as needed.

Brody et al. (2002) evaluated the benefits of self-management intervention in patients with AMD. Their 6-week intervention was led by a health professional and consisted of didactic instruction regarding basic information about AMD and rehabilitative strategies. It also contained a behavioral component that emphasized dealing with some of the challenges presented by AMD. Their data showed that the intervention group evidenced a significant improvement in mood 6 weeks post baseline and that this effect was most pronounced for those who were depressed at baseline. Intervention subjects also displayed improved function, and again this effect was most apparent for depressed subjects. A follow-up study at 6 months supports the intervention's sustained effects; benefits were greatest for subjects who were depressed at baseline. Importantly, the incidence of depression from baseline to 6 months was significantly lower in the intervention group. Discrepancies in long term effects between the Rovner and the Brody studies could be due to sampling differences. The

Rovner study did not include depressed subjects, while the Brody study did, and the intervention was most advantageous for this subgroup.

Evidence for the benefit of low-vision rehabilitation on depression is mixed. In a group of older people newly referred for low-vision rehabilitation, active participation in rehabilitation was related to a decrease in depressive symptoms over a 2-year period (Horowitz et al. 2005a). Girdler et al. (2010) compared the benefits of a usual care model of low-vision rehabilitation with an enhanced one. The enhanced intervention included an intensive group-level component whereby subjects were taught self-management strategies. Subjects in the enhanced intervention reported higher levels of activity engagement. At 12 weeks follow-up, 17 % of subjects in the enhanced intervention reported depressive symptoms, compared to 51 % of control subjects. This study shows that rehabilitation may not be enough to prevent and treat depression. Nevertheless, rehabilitation presents an optimal opportunity to improve function and possibly prevent or reduce depression.

AMD is a serious public health problem, robbing patients of independence and destroying their quality of life. As the population ages, greater numbers of Americans will be affected by this disease and subsequent depression. Thus, targeting depression, a major contributor to vision-related disability, is one strategy for maintaining independence and improving quality of life. Moreover, because depression and function are so closely intertwined in AMD, developing interventions that incorporate depression management into rehabilitation might be the best course of action.

## 14.3 Cognitive Decline in Age-Related Macular Degeneration

Many studies have linked vision loss with cognitive decline and physical disability. Crews and Campbell (2004) examined the 1994 Second Supplement on Aging involving 9,447 older persons and found that those with self-reported vision loss were 2.2 times more likely to be cognitively impaired than those without vision loss (Bäckman et al. 2003). Reyes-Ortiz et al. (2005), using the population-based Hispanic Established Populations for Epidemiologic Studies of the Elderly, found that objective measures of vision impairment were associated with cognitive decline (Bäckman et al. 2003; Breitner 2006). Data from the Health and Retirement Study revealed that untreated poor vision is associated with Alzheimer's disease (Rogers and Langa 2010). Persons with poor vision who did not visit an ophthalmologist had a 9.5-fold increased risk of Alzheimer's disease and a 5-fold increased risk of cognitive impairment but no dementia. By contrast, individuals with very good or excellent vision had a 63 % reduced risk of dementia. The North Carolina Established Populations for the Epidemiologic Studies of the Elderly Participants found that individuals with coexisting visual and cognitive impairment were at high risk for disability in instrumental activities of daily living [odds ratio (OR) 6.50], mobility (OR 4.04), basic activities of daily living (OR 2.84), and incident ADL disability (OR 3.66). These odds ratios were greater than the odds ratio associated with visual or cognitive impairment alone, indicating that visual and cognitive impairment contribute additively to disability risk (Whitson et al. 2007).

One mechanism that links cognitive decline and age-related changes in the visual system involves retinal vascular pathology. Because retinal and cerebral arterioles share similar pathologic processes, microvascular disease in the retina (e.g., microaneurysms, hemorrhages, and soft exudates) may reflect microvascular disease in the brain. To better understand this relationship, Lesage et al. (2009) examined retinal microvascular abnormalities and longitudinal changes in cognition in a community population (Wang et al. 2006). Participants underwent four cognitive assessments between 1990–1992 and 2004–2006, using the Word Fluency Test (which assesses language and executive function), the Digit Symbol Substitution Test (which assesses visual processing and psychomotor speed), and Delayed Word Recall (episodic memory) as well as retinal photography in 1993–1995. Over time,

individuals with retinopathy showed declines in executive function and psychomotor speed compared to those without retinopathy. This finding indicates that retinal vascular changes can serve as markers of the cerebral microvasculature and highlight the importance of cerebral microvascular disease as a cause of cognitive decline in older persons.

Other researchers have noted intriguing relationships between age-related macular degeneration (AMD) and cognitive decline (Klaver et al. 1999). Clemons et al. (2006) found that increased macular abnormalities and reduced vision were associated with lower cognitive function and that persons with vision acuity worse than 20/40 in both eyes were more likely to be cognitively impaired than persons with better visual acuity (Crews and Campbell 2004). Baker et al. (2009) studied the association of early AMD and cognitive function and dementia in the 2,088 persons aged 69–97 years who participated in the Cardiovascular Health Study. Cognitive function was assessed using the Digit Symbol Substitution Test and the Modified Mini-Mental Status Examination. After controlling for age, sex, race, and study center, persons with low Digit Symbol Substitution Test scores were more likely to have early AMD (OR, 1.38) than were persons with higher scores. In analyses controlling for education, systolic blood pressure, cholesterol level, diabetes mellitus, smoking status, and apolipoprotein E genotype, the association was even stronger (OR 2.00).

Similarities in the pathologies of AMD and Alzheimer's disease (AD) also suggest a linkage. Previous studies have observed degeneration of the optic nerve and retina in Alzheimer's disease (Clemons et al. 2006). In both AMD and AD, misfolded amyloid beta peptides accumulate and may play a central role in their onset (Yoshida et al. 2005). In AMD, an accumulation of drusen, which contain amyloid and the products of neurodegeneration, may promote further degenerative changes in the macula. In AD, increased production or reduced clearance of toxic amyloid oligomers leads to nerve cell dysfunction and cell loss. Some studies show that amyloid beta increases vascular endothelial growth factor (VEGF) and may lead to retinal pigment epithelium atrophy (Yoshida et al. 2005). There are also similarities in vascular risk factors for both AMD and AD, such as advanced age, hypertension, unhealthy diet, physical inactivity, obesity, and cigarette smoking. Both AMD and AD have also been linked to an increased risk of stroke (Mares et al. 2011; Middleton and Yaffe 2009; Tan et al. 2008). The Atherosclerosis Risk in Communities study found that persons with signs of late AMD were significantly more likely than those without AMD to have incident coronary heart disease over 10 years (30.9 % vs. 10.0 %) and higher incidence of stroke (4.1 % vs. 2.1 %) (Wong et al. 2006; 2007). The pathogenesis of both AMD and AD also appears to involve atherosclerosis, inflammation, and oxidative stress, which provide further evidence of shared pathogenetic mechanisms in the two diseases. Alternatively, vision loss may lead to cognitive decline via deafferentation of the visual system from the sensory cortex (Lindenberger and Baltes 1994). Interestingly, the two diseases apparently have different genetic risks (i.e., the APO 4 allele increases the risk for AD but decreases the risk for AMD) (Gandy 2005; Hinton et al. 1986).

Vision loss may also result in behavioral changes, such as relinquishing valued activities like reading and socializing, that indirectly and adversely affect neural function and can lead to or unmask incipient cognitive decline (Hendrie et al. 2006). To determine whether relinquishing cognitive, physical, and social activities is associated with an increased risk of cognitive decline in patients with AMD, we conducted a 3-year longitudinal study of older, nondemented patients with AMD who had participated in the Preventing Depression in AMD Trial (Rovner et al. 2007). This was a 12-month randomized controlled clinical trial comparing the efficacy of problem-solving treatment (PST) versus usual care to prevent depression in older patients with AMD. At the baseline visit of the clinical trial, we assessed the extent to which the 206 enrolled subjects had relinquished specific activities that

other research suggests prevent cognitive decline. Then 3 years later, we interviewed the 160 available knowledgeable informants of subjects who were originally enrolled in the clinical trial to ascertain whether subjects had declined cognitively. We tested the hypothesis that relinquishing more valued activities was associated with an increased risk for cognitive decline.

Over 3 years, 23 subjects (14.4 %) declined cognitively. Age, sex, education, decline in visual acuity, and number of dropped activities were associated with cognitive decline; each additional dropped activity increased the risk by 58 %. Subjects who relinquished 3 activities were 3.87 times [95 % CI 1.95, 7.76] more likely to become demented than subjects who relinquished no activities; those who relinquished 5 activities were 9.54 times [95 % CI 3.05, 30.43] more likely. A multivariate model demonstrated that the number of dropped activities was a powerful predictor of cognitive decline after controlling for relevant risk factors, particularly for subjects less than 80 years of age.

In AD, we know that cognitive activities such as reading or playing board games or musical instruments reduce the risk of dementia as do physical and social activities (Bennett et al. 2006; Sturman et al. 2005; Verghese et al. 2003; Wang et al. 2006; Wilson et al. 2002). The mechanism by which these activities maintain cognition is uncertain but may involve enhancing the brain's capacity to tolerate neuropathology (i.e., increased neural reserve) via beneficial effects upon neuroplasticity, neurogenesis, or cortisol regulation (Bird 2005; Schmidt et al. 2002). In our sample, activity loss may have triggered or hastened the onset of cognitive decline. Although other mechanisms are possible, our finding that activity loss is associated with cognitive decline in AMD underscores the importance of maintaining activities in the face of vision loss. This finding may also apply to patients with other chronic diseases that lead to the loss of or restrict participation in valued activities. If so, promoting optimal cognitive and physical health has wide relevance to the care of the growing population of older adults with chronic disabilities.

**Conclusion**

There are a number of possible mechanisms that link vision loss, due to AMD in particular, with cognitive decline. They include a common pathogenesis that involves shared histopathological features, inflammatory processes, and vascular risk factors.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable

## References

American Academy of Ophthalmology Retina/Vitreous Panel (2008) Age-related macular degeneration. American Academy of Ophthalmology (AAO), San Francisco. Available at www.AAO.org/ppp

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, D.C

Augustin A, Sahel JA, Bandello F et al (2007) Anxiety and depression prevalence rates in age-related macular degeneration. Invest Ophthalmol Vis Sci 48: 1498–1503

Bäckman L, Jones S, Small BJ et al (2003) Rate of cognitive decline in preclinical Alzheimer's disease: the role of comorbidity. J Gerontol B Psychol Sci Soc Sci 58:228–236

Baker ML, Wang JJ, Rogers S et al (2009) Early age-related macular degeneration, cognitive function, and dementia: the Cardiovascular Health Study. Arch Ophthalmol 127:667–673

Bennett DA, Schneider JA, Tang Y et al (2006) The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in older people: a longitudinal cohort study. Lancet Neurol 5:406–412

Bird TD (2005) Genetic factors in Alzheimer's disease. N Engl J Med 352:862–864

Breitner JCS (2006) Dementia—epidemiological considerations, nomenclature, and a tacit consensus definition. J Geriatr Psychiatry Neurol 19:129–136

Brody BL, Gamst AC, Williams RA et al (2001) Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. Ophthalmology 108:1893–1900

Brody BL, Roch-Levecq AC, Gamst AC et al (2002) Self-management of age-related macular degeneration and quality of life: a randomized controlled trial. Arch Ophthalmol 120:1477–1483

Brown G, Brown MM (2010) Let us wake the nation on the treatment for age-related macular degeneration. Curr Opin Ophthalmol 21:169–171

Byers AL, Yaffe K, Covinsky KE et al (2010) High occurrence of mood and anxiety disorders among older adults: the National Comorbidity Survey Replication. Arch Gen Psychiatry 67:489–496

Casten R, Rovner BW, Leiby BE et al (2010) Depression despite anti-vascular endothelial growth factor treatment of age-related macular degeneration. Arch Ophthalmol 128:506–508

Clemons TE, Rankin MW, McBee WL (2006) Cognitive impairment in the Age-Related Eye Disease Study: AREDS report no. 16. Arch Ophthalmol 124: 537–543

Cole MG (2005) Evidence-based review of risk factors for geriatric depression and brief preventive interventions. Psychiatr Clin North Am 28:785–803

Congdon N, O'Colmain B, Klaver CC et al (2004) Causes and prevalence of vision impairment among adults in the United States. Arch Ophthalmol 122:477–485

Crews JE, Campbell VA (2004) Vision impairment and hearing loss among community-dwelling older Americans: implications for health and functioning. Am J Public Health 94:823–829

Evans JR, Fletcher AE, Wormald RP (2007) Depression and anxiety in visually impaired older people. Ophthalmology 114:283–288

Gandy S (2005) The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. J Clin Invest 115:1–9

Gartlehner G, Hansen R, Thieda P et al (2007) Comparative effectiveness of second-generation antidepressants in the pharmacologic treatment of adult depression. Comparative Effectiveness Review No. 7. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Agency for Healthcare Research and Quality, Rockville. Available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Girdler SJ, Boldy DP, Dhaliwal SS et al (2010) Vision self-management for older adults: a randomised controlled trial. Br J Ophthalmol 94:223–228

Hayman KJ, Kerse NM, La Grow SJ et al (2007) Depression in older people: visual impairment and subjective ratings of health. Optom Vis Sci 84: 1024–1030

Hendrie HC, Albert MS, Butters MA et al (2006) The NIH Cognitive and Emotional Health Project Report of the Critical Evaluation Study Committee. Alzheimers Dement 2:12–32

Hinton DR, Sadun AA, Blanks JC et al (1986) Optic-nerve degeneration in Alzheimer's disease. N Engl J Med 315:485–487

Horowitz A, Reinhardt JP, Boerner K (2005a) The effect of rehabilitation on depression among visually disabled older adults. Aging Ment Health 9:563–570

Horowitz A, Reinhardt JP, Kennedy GJ (2005b) Major and subthreshold depression among older adults seeking vision rehabilitation services. Am J Geriatr Psychiatry 13:180–187

Jones GC, Rovner BW, Crews JE et al (2009) Effects of depressive symptoms on health behavior practices among older adults with vision loss. Rehabil Psychol 54:164–172

Klaver CC, Ott A, Hofman A et al (1999) Is age-related maculopathy associated with Alzheimer's Disease? The Rotterdam Study. Am J Epidemiol 150:963–968

Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16:606–613

Lam BL, Christ SL, Lee DJ et al (2008) Reported visual impairment and risk of suicide: the 1986–1996 national health interview surveys. Arch Ophthalmol 126:975–980

Lesage SR, Mosley TH, Wong TY et al (2009) Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. Neurology 73:862–868

Lindenberger U, Baltes PB (1994) Sensory functioning and intelligence in old age: a strong connection. Psychol Aging 9:339–355

Mares JA, Voland RP, Sondel SA et al (2011) Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. Arch Ophthalmol 129:470–480

Middleton LE, Yaffe K (2009) Promising strategies for the prevention of dementia. Arch Neurol 66:1210–1215

Mrazek P, Haggerty R (eds) (1994) Reducing risks for mental disorders: frontiers for prevention intervention research. National Academy Press, Washington, D.C

Nyman SR, Gosney MA, Victor CR (2009) The psychosocial impact of sight loss: an update of the evidence. Age Ageing 38:ii65

Radloff L (1977) The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401

Rees G, Tee HW, Marella M et al (2010) Vision-specific distress and depressive symptoms in people with vision impairment. Invest Ophthalmol Vis Sci 51:2891–2896

Reyes-Ortiz CA, Kuo WS, DiNuzzo AR et al (2005) Near vision impairment predicts cognitive decline: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly. J Am Geriatr Soc 53:681–686

Rogers MAM, Langa KM (2010) Untreated poor vision: a contributing factor to late-life dementia. Am J Epidemiol 171:728–735

Rovner BW, Casten RJ (2001) Neuroticism predicts depression and disability in age-related macular degeneration. J Am Geriatr Soc 49:1097–1100

Rovner BW, Casten R (2005) Stability of visual acuity measurement in depression. Am J Geriatr Psychiatry 13:255–258

Rovner BW, Ganguli M (1998) Depression and disability associated with impaired vision: the MoVies Project. J Am Geriatr Soc 46:617–619

Rovner BW, Casten RJ, Tasman WS (2002) Effect of depression on vision function in age-related macular degeneration. Arch Ophthalmol 120:1041–1044

Rovner BW, Casten RJ, Hegel MT et al (2006) Minimal depression and vision function in age related macular degeneration. Ophthalmology 113:1743–1747

Rovner BW, Casten RJ, Hegel MT et al (2007) Preventing depression in age-related macular degeneration. Arch Gen Psychiatry 64:886–892

Schmidt S, Klaver C, Saunders A et al (2002) A pooled case-controlled study of the apolipoprotein E (APOE) gene in age-related maculopathy. Ophthalmic Genet 23:209–223

Steffens DC, Fisher GG, Langa KM et al (2009) Prevalence of depression among older Americans: the Aging, Demographics and Memory Study. Int Psychogeriatr 21:879–888

Sturman MT, Morris MC, Mendes de Leon CF et al (2005) Physical activity, cognitive activity, and cognitive decline in a biracial community population. Arch Neurol 62:1750–1754

Tan JS, Wang JJ, Liew G et al (2008) Age-related macular degeneration and mortality from cardiovascular disease or stroke. Br J Ophthalmol 92:509–512

Verghese J, Lipton RB, Katz MJ et al (2003) Leisure activities and the risk of dementia in the elderly. N Engl J Med 348:2508–2516

Wang JY, Zhou DH, Li J et al (2006) Leisure activity and the risk of cognitive impairment: the Chongqing aging study. Neurology 66:911–913

Whitson HE, Cousins SW, Burchett BM et al (2007) The combined effect of visual impairment and cognitive impairment on disability in older people. J Am Geriatr Soc 55:885–891

Williams RA, Brody BL, Thomas RG et al (1998) The psychosocial impact of macular degeneration. Arch Ophthalmol 116:514–520

Wilson RS, Mendes de Leon CF, Barnes LL et al (2002) Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 287:742–748

Wong TY, Klein R, Sun C et al (2006) Age-related macular degeneration and risk for stroke. Ann Intern Med 145:98–106

Wong TY, Tikellis G, Sun C et al (2007) Age-related macular degeneration and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Ophthalmology 114:86–91

Yesavage JA, Brink TL, Rose TL et al (1983) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17:37–49

Yoshida T, Ohno-Matsui K, Ichinose S et al (2005) The potential role of amyloid beta in the pathogenesis of age-related macular degeneration. J Clin Invest 115:2793–2800

# Visual Disability in the Elderly: Implications for Visual Rehabilitation

# 15

Robert W. Massof, Maureen G. Maguire, Duane R. Geruschat, James T. Deremeik, Judith E. Goldstein, Mary Warren, Ann-Margret Ervin, Joan A. Stelmack, Pradeep Y. Ramulu, Barbara S. Hawkins, and Kevin D. Frick

## 15.1 Introduction

When visual system disorders result in bilateral visual impairments, patients have difficulty performing their customary activities and experience a diminished quality of life (West et al. 2002). Visual impairments increase patients' risk of falling (Ivers et al. 1998), injury (Salive et al. 1994), poor general health (Crews and Campbell 2001), depression (Casten et al. 2004), and even death (Pedula et al. 2006). Activity-limiting chronic visual impairments, collectively called "low vision," most often are caused by age-related visual system disorders, with age-related macular degeneration, glaucoma, diabetic retinopathy, and cataract leading the list (Congdon et al. 2004). Some visual system disorders, such as diabetic retinopathy, are manifestations of more general disorders that frequently produce co-disabilities. But most low vision patients are elderly, so comorbidities and co-disabilities from diseases unrelated to their visual system disorders are common (Ahmadian and Massof 2008). Thus, for a large portion of the low vision population, activity limitations from visual impairments are superimposed on and worsen activity limitations from comorbidities (Langelaan et al. 2009).

The prevalence of low vision in the USA is estimated to be greater than 3.5 million people (Congdon et al. 2004; Massof 2002). Eighty percent of those with low vision are over age 65 years. The prevalence of moderate and severe cases of low vision is 1.5 million Americans and the annual incidence in the USA is 240,000 (Massof 2002). In recent years, there have been dramatic advances in treatments of the diseases that cause low vision. Nevertheless, successful treatments typically result in chronic visual impairments, albeit not as severe as they would be without treatment (Chang et al. 2007; Bressler et al. 2010). Consequently, the

R.W. Massof, PhD (✉) • J.T. Deremeik, MA, CLVT
J.E. Goldstein, OD • P.Y. Ramulu, MD, MHS, PhD
B.S. Hawkins, PhD
Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University
School of Medicine, Baltimore, MD, USA
e-mail: bmassof@jhmi.edu

M.G. Maguire, PhD
Department of Ophthalmology, Wilmer Eye Institute, University of Pennsylvania
School of Medicine, Philadelphia, PA, USA

D.R. Geruschat, PhD, COMS, CLVT
Department of Graduate Studies in Vision Impairment, College of Education and Rehabilitation, Salus University, Elkins Park, PA, USA

M. Warren, PhD, OTR/L, SCLV
Department of Occupational Therapy, University of Alabama at Birmingham, Birmingham, AL, USA

A.-M. Ervin, PhD, MPH
Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

J.A. Stelmack, OD, MPH
Blind Rehabilitation Center, Hines VA Medical Center, Hines, IL, USA

K.D. Frick, PhD
Department of Health Policy and Management, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_15, 

prevalence and incidence of low vision is projected to double over the next 20 years as our population ages (Congdon et al. 2004; Massof 2002).

By definition, low vision is a chronic condition. To overcome activity limitations, low vision patients must learn to compensate for their chronic visual impairments and cope with the challenges they encounter in their daily lives, both within and outside their homes. Low vision rehabilitation and orientation and mobility instruction (LOVROM) aim to help patients live with low vision by providing tools and teaching strategies that will enable them to regain the ability to perform necessary daily activities, participate in society, and enjoy their lives. Existing LOVROM services employ four major approaches to intervention: (1) vision enhancement (e.g., magnification, illumination control, contrast stretching); (2) visual skills training (e.g., fixation or eccentric viewing training, visual awareness training, training in how to interpret visual information); (3) adaptations and accommodations (e.g., sensory substitution, environmental modifications, problem-solving strategies); and (4) patient and family education (e.g., coping strategies, accessing social and community services).

Our current system of LOVROM is an extension of a system developed more than 60 years ago to serve blind children in need of education and blind adults wanting to return to work. But the demographics of low vision and blindness have changed, with eight out of ten cases now over age 65. Consequently, the greatest demand for rehabilitation of the blind and visually impaired has shifted from the education and social service systems to the healthcare system, and the demand for services is now driven much more by low vision than it is by functional blindness. Over the past 15 years, LOVROM has been undergoing a gradual paradigm shift (Massof et al. 1995). Low vision rehabilitation (LVR) is now formally recognized as a healthcare service within the professions of ophthalmology (American Academy of Ophthalmology Vision Rehabilitation Committee 2007), optometry (American Optometric Association Consensus Panel on Care of the Patient with Low Vision 2007), and occupational therapy (Warren 2008). Nationwide coverage of LVR services by Medicare dates back only to 2002 (Centers for Medicare and Medicaid Services 2002). Coverage of services provided by orientation and mobility (O&M) specialists was included in the Medicare Low Vision Rehabilitation Demonstration Project (Bishop et al. 2010), but is not yet Medicare policy. And Medicare still explicitly excludes coverage of vision assistive equipment (VAE) for low vision patients (Morse et al. 2010).

Past studies agree that LVR and O&M services provided in the USA and other developed countries are minimally effective (Scott et al. 1999; Wolffsohn and Cochrane 2000; McCabe et al. 2000; Reeves et al. 2004; LaGrow 2004; Smith et al. 2005; Stelmack et al. 2006; de Boer et al. 2006; Hinds et al. 2007; Lamoureux et al. 2007; Walter et al. 2007; Court et al. 2011; Pierce et al. 2011). This conclusion does not mean that current LOVROM methods and VAE are not efficacious – there can be many reasons why efficacious interventions fail to be effective. For example, recent studies have reported high VAE abandonment rates (Dougherty et al. 2011) and poor rates of completion of LVR programs (Matt et al. 2011) by low vision patients, factors that could contribute to the observed failures of the effectiveness of LOVROM. LOVROM services provided by Blind Rehabilitation Centers (BRC) in the Veterans Health Administration (VA) produce large improvements in patients' functional ability (Stelmack et al. 2006). The BRCs provide low vision and blind rehabilitation services through intensive 1- to 6-week inpatient programs that include visual skills training, activities of daily living training, O&M instruction, communication skills instruction, manual skills training, computer access training, physical conditioning and recreation, and patient and family education and counseling (Maino 2001). These services are provided by a team of rehabilitation and healthcare professionals who work with the patient in 50-min sessions, 8 times/day, 5 days/week. The VA classifies VAE as prosthetic devices and covers the costs of all prescribed equipment for BRC patients. Typically, BRCs serve self-selected low vision patients who are highly motivated veterans with more severe visual impairments (e.g., visual acuity <20/100

in the better eye). Observational outcome studies at a VA BRC show with patient-reported outcome measures that the BRC's services are highly effective (Stelmack et al. 2006).

The VA Low Vision Intervention Trial (LOVIT) tested the effectiveness of an intensive outpatient LVR program that provided services modeled after the inpatient services in the BRC (Stelmack et al. 2008a). The participants were visually impaired veterans (visual acuity <20/100 to >20/500) who were eligible for BRC services and were on the BRC wait list. LOVIT participants were given 10–12 h of outpatient LVR services, provided mostly in the clinic over a period of 6 weeks (one session was provided in the patient's home), and homework assignments to complete between sessions (Stelmack et al. 2008b). As done for BRC patients, the VA covered the costs of all VAE prescribed to LOVIT participants. To prevent interruptions in the LVR schedule, free transportation was provided to participants who needed it. With these optimized conditions for LVR service delivery, participants in the LOVIT treatment group exhibited a large improvement in self-reported functional ability.

A census of private and state-sponsored LOVROM in the USA concluded that at the end of 2007, there were 1,228 private practices, agencies, or other non-VA entities, serving American low vision patients (Owsley et al. 2009). Generalizing from the responses to a survey of these services (50 % response rate), 43 % are in private optometry practices, 17 % in private ophthalmology practices, 4 % in university-based ophthalmology practices, 3 % in university-based optometry practices, 4 % in other healthcare settings, 11 % in private agencies, 8 % in state agencies, and the remaining 8 % are other non-healthcare system private entities. Overall, 96 % of low vision services provided in the private healthcare system report that they offer training in the use of VAE, 50 % say they offer eccentric viewing training, 33 % say they offer scanning training, 23 % report they sometimes make visits to the patients' homes, and 18 % say that O&M instruction is available.

Over the past decade, findings from observational outcome studies of private outpatient programs in several different countries concur that the effects of LOVROM are disappointingly small (Scott et al. 1999; Wolffsohn and Cochrane 2000; McCabe et al. 2000; Reeves et al. 2004; LaGrow 2004; Smith et al. 2005; Stelmack et al. 2006; de Boer et al. 2006; Hinds et al. 2007; Lamoureux et al. 2007; Walter et al. 2007; Court et al. 2011). All the LVR outcome studies, including the VA LOVIT, employed patient-reported outcome measures (PROM). But studies varied widely in their choice of PROM instruments and none, except LOVIT, employed an untreated control group. To compare studies, we converted their reported effects of intervention to Cohen's effect size (i.e., $d = \Delta\mu/\sigma$). Figure 15.1 illustrates effect sizes for different studies and different groups within studies. Three of the studies compared primary care outcomes to comprehensive care outcomes. Effects were small to medium for both types of LVR, and none of the studies saw any difference between the two types of care (Reeves et al. 2004; Court et al. 2011; Pierce et al. 2011). In the most direct comparison of private service outcomes to VA BRC outcomes, Stelmack et al. reported that one private practice-based and one university practice-based low vision service in the USA had effects of intervention that were one-fifth the size of the intervention effect for the VA BRC (Stelmack et al. 2006) (all three outcomes were estimated using the VA LV VFQ (Stemack et al. 2004)).

The obvious differences between VA and private healthcare system services that likely explain much of the large differences in outcomes include:

1. The VA pays all costs of prescribed VAE; in the private healthcare system, patients must pay 100 % of VAE costs. Consequently many patients do not acquire prescribed VAE.
2. The VA programs are comprehensive and intensive; the private healthcare system programs concentrate on low vision device training.
3. Service delivery in VA programs is consistent and complete; programs in the private healthcare system are inconsistently attended and often not completed by patients. Typical BRC patients are admitted as VA hospital inpatients for 4 weeks and stay focused exclusively on the rehabilitation program. LOVIT patients

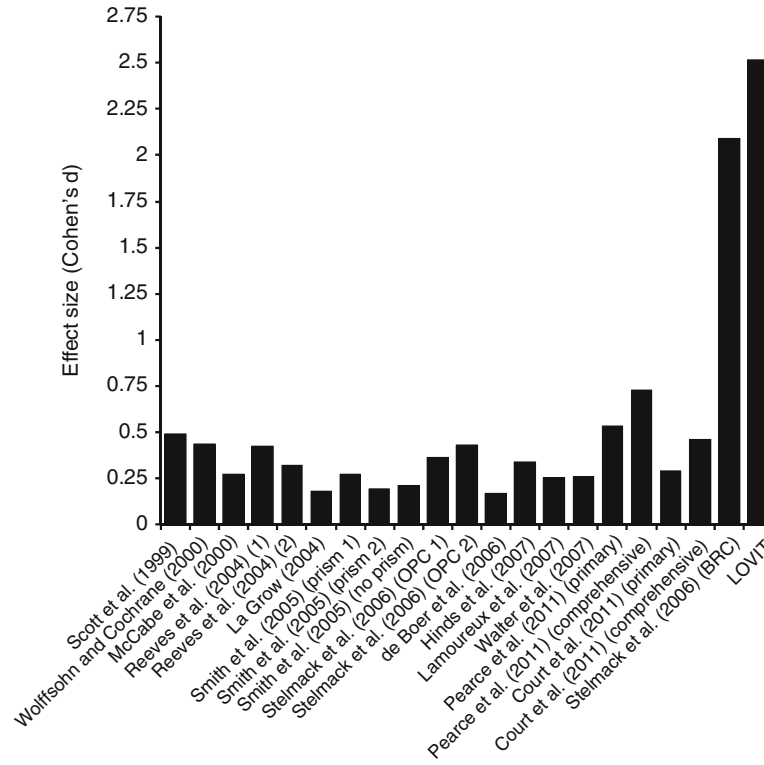


**Fig. 15.1** LVR effect sizes for different clinical outcome studies and groups within studies

had transportation services provided so that they did not miss their rehabilitation sessions in the clinic, were required to complete homework exercises between sessions to stay focused on their therapy, and had a home visit. In the private healthcare system, patients must provide their own transportation to the outpatient clinic for rehabilitation sessions (which is difficult because most patients cannot drive, appointments frequently are missed, and the dropout rate is very high), and services provided in the patient's home are rare, so inconsistent and incomplete services are common.

4. The VA BRC routinely provides O&M instruction; O&M instruction is rare in the private healthcare system.

Given these differences, it is reasonable to propose that private outpatient low vision services would be more effective if the services were comprehensive, intensive, well targeted to the patients' needs, and made consistent by accommodating physical constraints imposed on patients by their health, mobility, and availability of assistance.

## 15.2 Optimizing Outpatient Low Vision Rehabilitation with a Feasible Service Delivery Model

LVR practitioners in the private healthcare system employ one of three service delivery models. First is the "primary care model," (Nowakowski 1994) in which clinicians dispense VAE, usually magnifiers, and train the patient in the clinic how to use them. This model is described in the American Optometric Association's low vision clinical practice guideline (American Optometric Association Consensus Panel on Care of the Patient with Low Vision 2007) and is the model most commonly employed in optometric practices (Owsley et al. 2009). At the next level of service, eccentric viewing training and other types of visual skills instruction are offered in the clinic, in addition to training the patient to use VAE. Occasionally, some LVR therapists may make visits to some patients' homes in addition to providing in-clinic services. This second LVR

service delivery model, which is most commonly employed in private ophthalmology practices, in practices associated with academic institutions, and in practices associated with rehabilitation agencies, often is called the "comprehensive care model" (Markowitz 2006). This model is described in the American Academy of Ophthalmology's Preferred Practice Pattern for LVR (American Academy of Ophthalmology Vision Rehabilitation Committee 2007) and is covered by Medicare part B as long as the LVR services are provided by a trained occupational therapist (OT) (Centers for Medicare and Medicaid Services 2002). The third LVR service delivery model is the "home healthcare model." This model, which rarely is employed, requires low vision patients to be referred by a physician to a licensed home healthcare agency, and all LVR services are provided in the patient's home within a 60-day episode. Services provided under the home healthcare model are covered by Medicare part A for patients who meet the requirements of being homebound (most do because they cannot drive or travel independently) and having at least one systemic disorder diagnosis besides low vision (70–80 % of low vision patients meet this requirement (Medicare Benefits Policy Manual 2011)).

There have been no formal outcome studies performed on the home healthcare model for LVR. At least two companies (Low Vision Works home page; HomeSight home page) have offered consulting services to home healthcare agencies with the aim of adding LVR to the agency's list of specialty services. The consulting companies train their clients' OTs and home healthcare nurses to provide LVR services and assist their clients with marketing LVR services to referring physicians and to the public. The LVR services provided by the agencies target patients with moderate and severe low vision who are homebound and have at least one other systemic disorder and thus meet eligibility requirements for Medicare coverage. All LVR services are provided in the patients' home over a period of 60 days. The agencies must provide their LVR services pursuant to a physician's orders (Goldberg-Dey et al. 2011). The consulting companies and their client agencies claim excellent LVR outcomes, but to date, nothing more than testimonials has been offered as supporting evidence.

There are two compelling reasons why providing LVR services to patients within their home instead of the clinic should be optimal. First, unlike most medical rehabilitation, which is aimed at restoring function to normal levels, LVR focuses on enabling patients to continue engaging in everyday activities despite their chronic visual impairments. Most people with low vision live in their own homes or apartments and are responsible for meeting their daily needs within this specific environment (O'Connor et al. 2008). The type of lighting, contrast, and clutter within the patient's environment can either facilitate or inhibit her/his ability to use remaining vision to perform daily tasks (Haymes and Lee 2006; Brunnstroom et al. 2004; Watson 2001; Wald et al. 1999). Adequate simulation of the specific qualities of the home environment within the artificial confines of the clinic is difficult. Medicare, the main third-party payer of LVR, encourages providing rehabilitation services in the home and covers home services under both parts A and B. A report on LVR completed for the Centers for Medicare and Medicaid Services suggested adoption of the home healthcare model as an appropriate and effective method of providing LVR to Medicare beneficiaries (Bishop et al. 2010).

Second, low vision patients experience unique transportation issues that create barriers to participating in clinic-based rehabilitation programs. The visually impaired person rarely drives because of poor vision (DeCarlo et al. 2003; Massof et al. 2007a), and frequently his or her spouse also does not drive. This situation forces reliance on adult children, friends, or service organizations who often are unable to be a consistent source of transportation because of family and work obligations (Goldstein et al. 2012). Thus, missed appointments and dropping out of LVR service are common. Providing in-home services should improve the likelihood of consistent participation in the LVR services.

The home healthcare model promises to be an optimal approach to LVR in the private sector

because it increases the frequency and intensity of service and increases the likelihood the patient will complete the planned LVR. Also, the patient is not required to transfer skills learned in the clinic to a different environment and set of circumstances in the home. All LVR services can be customized to accommodate the unique characteristics of each patient's home environment, and environmental modifications can be made to increase safety and accommodate the patient's needs. The home healthcare model of LVR is feasible because it is supported by Medicare part B, and when implemented through licensed home healthcare agencies, it also is supported by Medicare part A. But, despite all its pluses, the home healthcare model does not address problems the patient has functioning outside the home.

## 15.3 Providing O&M Instruction to Low Vision Patients as a Healthcare Service

Much of the emphasis of LVR currently is directed at restoring reading function and achieving goals related to activities normally performed inside the home (Markowitz 2006; Bachelda and Harkins 1995). Most activities performed outside the home require the patient to be mobile. In the private healthcare system, O&M instruction typically is not included in the LVR regimen (Owsley et al. 2009). Indeed, OTs consider O&M instruction to be outside their scope of practice (Riddering 2008). But there is strong documentation that people with low vision, even those with moderate visual impairments, experience functional limitations with mobility. (Marron and Bailey 1982; Leat and Lovie-Kitchin 2008) More important, because most low vision patients are elderly (Massof 2002; Owsley et al. 2009), they are at increased risk of injury from falls and accidents and increased risk of physical and mental health problems from reduced activity levels (Salive et al. 1994; Crews and Campbell 2001). The mobility limitations of people with low vision potentially could be ameliorated with O&M instruction. Although most O&M specialists are trained to work with low vision clients, the lay public, third-party payers, and many eye care professionals assume that O&M instruction is needed only by people who are functionally blind and assume that it is not a healthcare service. For example, in a recent poll of 120 optometrists, we asked respondents at what visual acuity they would first consider referring a visually impaired patient for O&M instruction; 93 % responded that they would require the patient to be legally blind.

Improving mobility function is medically necessary for older low vision patients. The Safety of Seniors Act of 2007 has made preventing falls and increasing physical activity levels in the older population high priority health agenda items in the USA (Safety of Seniors Act of 2007). The maintenance of balance and postural stability becomes more difficult with age. Besides an increased prevalence of age-related musculoskeletal disorders, such as arthritis and peripheral artery disease, normal aging results in neurodegenerative changes in muscle and joint somatic receptors that interfere with accurate knowledge of the degree of flexion of the limbs and sense forces on the skin, muscles, and joints (Skinner et al. 1984). Also typical with aging is a degeneration of hair cells in the vestibular organ, which interferes with sensing angular and linear acceleration (Ochs et al. 1985). These losses put a greater demand on the visual system to provide sensory information needed to maintain balance – even moderate visual impairments can lead to increased postural instability (Tobis et al. 1990; Turano et al. 1996). Older people with low vision have slower walking speeds (Patel et al. 2006), abnormal gait, and increased incidence of stumbles and near falls (Spaulding et al. 1994). Epidemiological studies show that even mild visual acuity loss increases the risk of falling (Ivers et al. 1998; Klein et al. 2003; Abdelhafiz and Austin 2003), with fall prevalence ratios (relative to 20/20 visual acuity) of 2 for visual acuity <20/30 in the better eye. Relative to older people with 20/20 acuity, the risk of hip fractures doubles for older people with visual acuity in the 20/30–20/40 range, triples for visual acuity in the 20/50–20/70 range, and quadruples for older people

with visual acuity <20/70 (Dargent-Molina et al. 1996). More than 50 % of accidental deaths in the older population are from falls. Relative to people with 20/20 visual acuity, the death rate for older people increases independently of age and comorbidities by 20 % for people with visual acuity of 20/25 in the better eye, 35 % for people with visual acuity of 20/30, and 60 % for people with visual acuity <20/30 (Pedula et al. 2006).

Approximately one-third of the older population reports a fear of falling (Tinetti et al. 1994; Arfen et al. 1994; Vellas et al. 1997), and about 10 % report an intense fear of falling (Howland et al. 1998). Fear of falling is associated with decreased activity levels due to self-limitations (Howland et al. 1998; Li et al. 2003; Scheffer et al. 2008). Older people with low vision are 3.7 times more likely to report a strong fear of falling than do normally sighted people in the same age group (Arfen et al. 1994). Relative to people with 20/20 visual acuity, the prevalence of physical limitations on activities (assessed with walking tests, balance tests, and stair climbing tests) ranges from 30 % greater in people with mild visual impairments, to twice as great in people with severe visual impairments (West et al. 2002).

Recently, our group monitored physical activity levels in visually impaired AMD patients and normally sighted age-matched AMD patients. A 0.1 log MAR decrement in visual acuity was associated with a 6.1 % decrease in daily steps. AMD patients were 3.5 times more likely not to leave their home in a day and took 43 % fewer steps per day than controls (Chan et al. 2011).

O&M instruction long has been identified with teaching blind people how to travel independently using a long white cane. But the field of O&M instruction has advanced considerably over the past 70 years to include a wide array of approaches to increasing mobility (Wiener and Siffermann 2010). In the late 1960s, O&M instruction was extended from solely adults to blind children through schools for the blind. Beginning in the mid-1970s, O&M instruction was offered to people with severe low vision. Instruction methods evolved as the served population expanded and diversified; with the addition of low vision clients, techniques were developed to optimize the use of remaining vision and interpret visual information in the scene. From a health perspective, by improving mobility function, the O&M specialist explicitly addresses the healthcare aims of increased safety, increased physical activity, and increased socialization and community integration.

Low vision patients need to improve their mobility, but evidence of the effectiveness of O&M instruction is contradictory and based on studies with weak methodology and/or very small numbers:

1. Geruschat and De l'Aune compared outcomes of O&M instruction for three groups of VA Blind Rehabilitation Center (BRC) patients: those who used vision alone to travel (10 participants), those who used vision and cane to travel (7 participants), and those who used cane alone to travel (2 participants) (Geruschat and De l'Aune 1989). Outcome measures consisted of instructors' scores of errors participants made on a mobility course. The investigators observed a significant improvement in scores post-rehabilitation for all groups combined.
2. Straw et al. performed the only randomized controlled trial of O&M instruction. The first part of the study looked at 35 legally blind (low vision) participants (mean age 76) who were assigned to a treatment or control group. The treatment group received 10–12 weeks of 90 min/week O&M instruction targeting the areas of orientation, independent mobility, and sighted guide mobility. The comparison group received fitness exercises as placebo training. The outcome measure consisted of performance scores in each training area that were assigned by an expert O&M instructor (Straw et al. 1991). The study was repeated with 32 functionally blind participants (mean age = 77) (Straw and Harley 1991). The baseline scores were lower for the functionally blind group than for the low vision group. A significant improvement in the overall O&M score was seen for the functionally blind group, but not for the low vision group.

3. Soong et al. conducted a study that compared a group of low vision patients (19) who received O&M instruction, including how to use the long cane, to another group of patients (18) who received no training (Soong et al. 2001). The outcome measures were walking speed and counts of mobility errors on a course. These investigators saw no effect of training.
4. Ramsey et al. looked at the effects of mobility training on gait and balance in an uncontrolled study (Ramsey et al. 2003). Six VA BRC patients, who were approximately 70 years old and had visual acuity of 20/200 or less in the better eye, were participants. Baseline data were collected within 1 week of admission to the BRC, and follow-up data were collected at discharge. The investigators employed six performance measures (gait velocity, stride length, stride rate, double stance time, the Berg Balance test, and hand-grip strength). They also used a self-report questionnaire, the Fall Efficiency Scale (FES), to estimate fear of falling. The investigators concluded that O&M instruction had no effect on any of the measures.
5. Kuyk et al. employed Turano's independent mobility questionnaire (Turano et al. 2002) to estimate the effects of O&M instruction on 128 VA Blind Rehabilitation Center patients, more than half of whom had age-related macular degeneration (Kuyk et al. 2004). The investigators reported significant improvements in average response rank scores for each item. The investigators also saw an increase in patient-reported confidence with travel ability, a decrease in the percentage of patients who had fallen, and a decrease in the average number of falls among those who had fallen previously, but no change in the prevalence of fear of falling.

The indisputable fact is that the ever-growing low vision population has substantial functional problems due to limitations in mobility. While O&M instruction appears to be an obvious solution, perceptions by physicians and patients that O&M services are meant only for blind children and for blind adults seeking employment, the absence of a feasible reimbursement system, as well as the absence of definitive evidence of the effectiveness of this type of rehabilitation have resulted in little utilization of O&M services. The literature strongly supports the thesis that low vision patients have a medical need for the professional services of an O&M specialist, which are distinctly different from the services offered by OTs and other low vision rehabilitation professionals. O&M instruction provided to low vision patients by an O&M specialist should improve their mobility function and balance. Potential downstream benefits include decreased risk of injury, decreased fear of falling, and increased levels of physical activity, which ultimately could lead to decreased morbidity and mortality and increased life space and community integration. Overall, the functional gains from O&M services have the potential to improve the lives of low vision patients, which would manifest as measurable gains in quality of life that could inform health policy decisions. Past studies of O&M instruction outcomes produced equivocal results, so there is true equipoise with respect to evidence, even though there are individuals with strong personal opinions for and against the value of O&M instruction for low vision patients. Previous studies had weak designs and were grossly underpowered (Vigili and Rubin 2003). Nevertheless, the results were encouraging, especially the results of the Kuyk et al. (2004) study, which used a self-report measure.

## 15.4 Approaches to Measuring the Effectiveness of LOVROM

There are many measurement strategies from which to choose:

1. Performance measures in the clinic such as reading speed (Legge et al. 1989), reading comprehension (Watson and Wright 1996), walking speed (Geruschat et al. 1998), navigation accuracy (Turano et al. 2004), and accuracy/speed of performing visual motor tasks (Owsley et al. 2001)
2. Real-world performance measures (e.g., physical activity levels in the home environment by accelerometers) (Chan et al. 2011)

3. Rating of patient performance by clinicians (Babcock-Parziale et al. 2005), as more commonly done in occupational and physical therapy with instruments such as the Functional Independence Measure (FIM) (Granger et al. 1998) and the Assessment of Motor and Process Skills (AMPS) (Park et al. 1994)
4. Patient self-report instruments such as visual function (Massof 2007) and quality of life (Wolffsohn and Cochrane 2000) rating scale questionnaires

The limitation suffered by most clinic-based performance measures and ratings by expert judges is that they constitute observations of what the patient can do on surrogate tasks at that moment, under artificial conditions; they do not measure what the patient actually does in everyday life. Consequently, the most common performance measures and clinician ratings can be used to measure the efficacy of an intervention (how well an intervention works under ideal circumstances), but cannot be used to measure its effectiveness (how well an intervention works in "real-world" settings).

When choosing an outcome measure for visual rehabilitation, one must keep in mind that, with the exception of improved refractive error correction, LOVROM services and VAE do not change the patient's vision. Unlike medical and surgical procedures, which can improve visual acuity in some conditions, such as cataract, and have a positive effect on many aspects of the patient's life, the effects of LVR are activity-specific (e.g., a table top CCTV magnifier may improve the patient's ability to perform the activity of reading mail, but have no effect on the patient's ability to perform the activity of reading price tags in a store). Consequently, outcome measures must have content that is chosen carefully to be relevant and responsive to the effects of LOVROM. Also, VAE, adaptations, visual skills training, and patient education require patients to participate, not simply comply, and they require the patient to compromise (e.g., magnification is accomplished at the expense of field of view and/or working distance; adaptations and visual skills training require the patient to give up familiar routines and develop new habits). Consequently, LOVROM outcome measures also must be sensitive to individual patient preferences and willingness to change because those factors will affect the importance and relevance of the measurement instrument's content. Finally, patients may be capable of performing activities but do not do so because they lack confidence or are fearful. Successful interventions, particularly O&M instruction, may achieve their effects, at least in part, by building the patient's confidence and reducing fear. Thus, the optimal outcome measure also must be responsive to changes in psychological variables that contribute to the patient's activity limitations.

When evaluating patients, LVR therapists and O&M instructors do not simply assess functional abilities. Rather, they identify activities that are important to the patient and are difficult or impossible for the patient to perform with the current approach to performing the activity. Instead of intervening to restore a standard array of functional abilities, many of which may have limited or no relevance to a specific patient, LVR therapists and O&M instructors are goal directed; they employ individualized intervention strategies based on vision enhancement, adaptations, and accommodations to make targeted activities easier to perform despite the patient's limited functional capabilities. For accurate assessment of the effects of services provided under goal-directed intervention, an approach that can capture improvement in attaining goals is required.

Measuring the effectiveness of goal-directed rehabilitation requires an adaptive patient-centered approach. Goals are the reasons for performing activities. Goals are attained by completing a set of specific cognitive and motor tasks (Massof 1995). For a given goal, the specific tasks that must be completed may vary among patients. For example, to attain the goal of cooking daily meals may require one patient to read recipes, cut or chop food, measure ingredients, set stove and oven controls, pour liquids without spilling, and judge when the food has finished cooking. For another patient, cooking daily meals may require only finding the correct package in the freezer, reading the cooking instructions, and setting the controls on the microwave. For either example, if the individual tasks cannot be

performed, the goal cannot be attained. The LVR therapist may train the first patient to use a magnifier to read recipes, advise the patient to buy precut or pre-chopped food, mark measuring spoons with colored tape, use Velcro tape or Hi-Marks to label common stove and oven settings, show the patient how to use a funnel to pour liquids, and teach the patient how to use a large print timer and/or talking food thermometer to judge when the food has finished cooking. Such task adaptations, or accommodations in the case of cutting or chopping food, make the component tasks easier to perform, or obviate them, so that the parent goal can be attained. For the second patient, the intervention is much simpler – organize the freezer and mark the packages with large print labels, teach the patient to use a magnifier to read the cooking instructions, and mark the microwave controls with Hi-Marks or other markers. In both cases, successful rehabilitation means that the patient can attain the goal of cooking daily meals; but in neither case have the patient's functional capabilities, which are traits of the patient, been improved.

The Activity Inventory (AI) (Massof et al. 2005a, b; 2007b) is an adaptively administered patient-reported outcome measure of the effects of goal-directed interventions. The AI has an item bank with 50 goals and a total of 460 tasks nested under the goals. The patient is presented with a goal and asked to rate its importance (not important, slightly important, moderately important, or very important). Whenever a patient responds that the goal is not important, the interviewer moves on to the next goal; otherwise the patient is asked to judge the difficulty of attaining the goal, and an ease of performance rank score is assigned to the response (4, not difficult; 3, somewhat difficult; 2, moderately difficult; 1, very difficult; or 0, impossible). Whenever a patient responds that the goal is not difficult, the interviewer moves on to the next goal; otherwise the patient is asked to rate the difficulty of each task nested under the goal (using the same five response categories) or respond that the task is "not applicable." After all of the tasks under the goal have been rated, the interviewer moves on to the next goal. The AI is well validated and well studied and is or has been used as the primary outcome measure in four clinical trials (Pierce et al. 2011; Rovner et al. 2011; U.S. National Institutes of Health 2009; U.S. National Institutes of Health 2006) and in prospective clinical outcome studies in the UK; (Tabrett and Latham 2011) a Dutch version (D-AI) is being validated to be used as a clinical outcome measure in the Netherlands (Bruijning et al. 2010).

Item responses are interpreted with a general scaling theory, and measures are constructed from responses to sets of AI items using Rasch analysis. At the time of the baseline assessment, each low vision patient has some amount of functional ability. Depending on the visual requirements, each goal and task in the AI item bank demands of the person some minimum amount of functional ability in order to be performed with a criterion level of ease. When the patient is asked to rate the difficulty of an item, the patient judges the difference between his/her functional ability and the functional ability required to perform the goal or task described by that item. This difference is called "functional reserve" (Massof 1998).

Interventions can have three possible effects that manifest as increases in functional reserve for a given patient (Massof 2013). First, there could be an increase in the patient's functional ability (e.g., due to correction of refractive error). Second, there could be a systematic reduction in the patient's response criteria (e.g., due to an increase in the patient's confidence or reduction in the patient's fear). Third, because of adaptations and/or vision enhancement, there could be a decrease in the functional ability demanded of the patient by selected items. Vision enhancement and task adaptations are expected to decrease functional ability demands of targeted tasks, resulting in an overall increase in average functional reserve across tasks; accommodations are expected to reduce the number of difficult or impossible tasks involved in a targeted goal by making obviated tasks "not applicable," which also increases average functional reserve across tasks (Massof 2013).

Because LVR and O&M instruction address different goals, they require different outcome measures. Some goals such as cooking daily

meals, managing personal finances, and dressing typically are performed inside the home. Other goals such as shopping, attending church, and attending meetings are performed outside the home. Inside-the-home goal activities depend heavily on patients' reading, visual information processing, and visual motor function and depend to a lesser extent on patients' mobility. Outside-the-home goal activities depend heavily on mobility but also on the other functions that are limited by visual impairments. The LVR therapist addresses goal activities that normally are performed in the patient's home; the O&M specialist addresses goal activities that normally are performed outside the home. Ideally, outcome measures of both types of services would be on the same scale but selectively responsive to the attainment of respective inside-the-home or outside-the-home goals that are indentified by the individual patient.

## Conclusions

The Western world's population is aging and both the incidence and prevalence of vision disabilities from age-related eye diseases will double over the next 20 years. Studies show that low vision not only results in reduced functional capabilities and reduced quality of life but also increases the risk of premature morbidity and mortality. Although the Low Vision Intervention Trial demonstrated that under optimal conditions low vision rehabilitation can restore the patient's ability to function in daily life, other studies conclude that the effectiveness of current low vision rehabilitation practices is weak outside the US VA healthcare system. Furthermore, the supply of low vision rehabilitation services and qualified service providers is inadequate to meet the current demand and third-party payment policies discourage growth in supply. The authors advocate a service delivery model that emphasizes the provision of low vision rehabilitation and orientation and mobility instruction in the patient's home and in the patient's community. It will be necessary to conduct rigorous clinical research to prove the effectiveness and value of such a service delivery model and effect changes in healthcare policies. But future studies will have to accommodate the individualized nature of LOVROM and very carefully choose outcome measures that are responsive to the achievement of the individual rehabilitation goals for each patient.

**Acknowledgments** Conflict of interest: none; Ethical standards: Informed consent – not applicable: Animal rights – not applicable

## References

Abdelhafiz AH, Austin CA (2003) Visual factors should be assessed in older people presenting with falls or hip fracture. Age Ageing 32:26–30

Ahmadian L, Massof RW (2008) Impact of general health status on validity of visual impairment measurement. Ophthalmic Epidemiol 15:345–355

American Academy of Ophthalmology Vision Rehabilitation Committee (2007) Preferred Practice Pattern: vision rehabilitation for adults. American Academy of Ophthalmology, San Francisco

American Optometric Association Consensus Panel on Care of the Patient with Low Vision (2007) Optometric clinical practice guideline: care of the patient with visual impairment (low vision rehabilitation). American Optometric Association, St. Louis

Arfen CL, Lach HW, Birge SJ, Miller JP (1994) The prevalence and correlates of fear of falling in elderly persons living in the community. Am J Public Health 84:565–570

Babcock-Parziale J, McKnight PE, Head DN (2005) Evaluating psychometric properties of a clinical and a self-report blind rehabilitation outcome measure. J Rehabil Res Dev 42:487–498

Bachelda JM, Harkins D Jr (1995) Do occupational therapists have a primary role in low vision rehabilitation? Am J Occup Ther 49:927–930

Bishop C, Perloff J, Meagher J, Ritter G, Leutz W (2010) Evaluation of the low vision rehabilitation demonstration. Claims analysis. Final Report, CMS Contract No. 500-00-0031. Web access: http://www.cms.gov/Reports/Downloads/Bishop_LowVisiDemoClaims_2010.pdf. Accessed on Mar 18, 2013

Bressler NM, Chang TS, Suner U et al (2010) Vision-related function after ranibizumab by better or worse-seeing eye: clinical trial results from MARINA and ANCHOR. Ophthalmology 117:747–756

Bruijning JE, van Nispen RM, van Rens GH (2010) Feasibility of the Dutch ICF Activity Inventory: a pilot study. BMC Health Serv Res 10:318

Brunnstroom G, Sorensen S, Alsterstad K, Sjostrand J (2004) Quality of light and quality of life – the effect of lighting adaptation among people with low vision. Ophthalmic Physiol Opt 24:274–280

Casten RJ, Rovner BW, Tasman W (2004) Age-related macular degeneration and depression: a review of recent research. Curr Opin Ophthalmol 15:181–183

Centers for Medicare and Medicaid Services (CMS) (2002) Provider education article: medicare coverage of rehabilitation services for beneficiaries with vision impairment. Program Memorandum AB-02-078, 29 May 2002

Chan ES, Hochberg C, Maul E, Ferrucci L, Friedman DS, Ramulu P (2011) Objective quantification of physical activity and travel outside the home in age-related macular degeneration. Invest Ophthalmol Vis Sci 52:E-abstract 1911

Chang TS, Bressler NM, Fine JT, Dolan CM, Ward J, Klesert TR (2007) Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration. Arch Ophthalmol 125: 1460–1469

Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P (2004) Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 122(4):477–485

Court H, Ryan B, Bunce C, Margrain TH (2011) How effective is the new community-based Welsh low vision service? Br J Ophthalmol 95:178–184

Crews JE, Campbell VA (2001) Health conditions, activity limitations, and participation restrictions among older people with visual impairments. J Vis Impair Blind 95:453–467

Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, Meunier PJ, Breart G et al (1996) Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 348:145–149

de Boer MR, Twisk J, Moll AC et al (2006) Outcomes of low-vision services using optometric and multidisciplinary approaches: a non-randomized comparison. Ophthalmic Physiol Opt 26:535–544

DeCarlo DK, Scilley K, Wells J, Owsley C (2003) Driving habits and health-related quality of life in patients with age-related maculopathy. Optom Vis Sci 90:207–213

Dougherty BE, Kehler KB, Jamara R et al (2011) Abandonment of low vision devices in an outpatient population. Optom Vis Sci 88:1283–1287

Geruschat DR, De l'Aune W (1989) Reliability and validity of O&M instructor observations. J Vis Impair Blind 83:457–460

Geruschat DR, Turano KA, Stahl JW (1998) Traditional measures of mobility performance and retinitis pigmentosa. Optom Vis Sci 75:525–537

Goldberg-Dey J, Johnson M, Pajerowski W, Tanamor M, Ward A (2011) Home Health Study Report. Report to CMS HHSM-500-2010-00072C

Goldstein JE, Massof RW, Deremeik JT, Braudway S, Jackson ML, Kehler KB, Primo SA, Sunness JS, LOVRNET Study Group (2012) Baseline traits of low vision patients served by private outpatient clinical centers in the United States. Arch Ophthalmol 130:1028–1037

Granger CV, Deutsch PC, Linn RT (1998) Rasch analysis of the Functional Independence Measure (FIM) Mastery Test. Arch Phys Med Rehabil 79:52–57

Haymes SA, Lee J (2006) Effects of task lighting on visual function in age-related macular degeneration. Ophthalmic Physiol Opt 26:169–179

Hinds A, Sinclair A, Park J et al (2007) Impact of an interdisciplinary low vision service on the quality of life of low vision patients. Br J Ophthalmol 87:1391–1396

HomeSight home page. http://www.homesight.biz/. Accessed on Mar 18, 2013

Howland J, Lachman ME, Peterson EW, Cote J, Kasten L, Jette A (1998) Covariates of fear of falling and associated activity curtailment. Gerontologist 38:549–555

Ivers RQ, Cumming RG, Mitchell P, Attebo K (1998) Visual impairment and falls in older adults: the blue Mountains Eye Study. J Am Geriatr Soc 46:58–64

Klein BE, Moss SE, Klein R, Lee KE, Cruickshanks KJ (2003) Associations of visual function with physical outcomes and limitations 5 years later in an older population: the Beaver Dam Eye Study. Ophthalmology 110:644–650

Kuyk T, Elliott JL, Wesley J, Scilley K, McIntosh E, Mitchell S, Owsley C (2004) Mobility function in older veterans improves after blind rehabilitation. J Rehabil Res Dev 41:337–346

LaGrow SJ (2004) The effectiveness of comprehensive low vision services for older persons with visual impairments in New Zealand. J Vis Impair Blind 98:679–692

Lamoureux EL, Pallant JF, Pesudovs K et al (2007) The effectiveness of low-vision rehabilitation on participation in daily living and quality of life. Invest Ophthalmol Vis Sci 48:1476–1482

Langelaan M, de Boer MR, van Nispen RMA, Wouters B, Moll AC, van Rens GHMB (2009) Change in quality of life after rehabilitation: prognostic factors for visually impaired adults. Int J Rehabil Res 32:12–19

Leat SJ, Lovie-Kitchin JE (2008) Visual function, visual attention, and mobility performance in low vision. Optom Vis Sci 85:1049–1056

Legge GE, Ross JA, Luebker A, LaMay JM (1989) Psychophysics of reading. VIII. The Minnesota low-vision reading test. Optom Vis Sci 66:843–853

Li F, Fisher J, Harmer P, McAuley E, Wilson NL (2003) Fear of falling in elderly persons: association with falls, functional ability, and quality of life. J Gerontol B Psychol Sci Soc Sci 58:P283–P290

Low Vision Works home page. http://www.lowvisionworks.com/. Accessed on Mar 18, 2013

Maino JH (2001) Low vision and blindness rehabilitation in the VA: inpatient rehabilitation. In: Massof RW, Lidoff L (eds) Issues in low vision rehabilitation: service delivery, policy, and funding. AFB Press, New York

Markowitz SN (2006) Principles of modern low vision rehabilitation. Can J Ophthalmol 41:289–312

Marron JA, Bailey IL (1982) Visual factors and orientation-mobility performance. Am J Optom Physiol Opt 59:413–426

Massof RW (1995) A systems model for low vision rehabilitation. 1. Basic concepts. Optom Vis Sci 72: 725–736

Massof RW (1998) A systems model for low vision rehabilitation. II. Measurement of vision disabilities. Optom Vis Sci 75:349–373

Massof RW (2002) A model of the prevalence and incidence of low vision and blindness among adults in the U.S. Optom Vis Sci 79:31–38

Massof RW (2007) An interval-scaled scoring algorithm for visual function questionnaires. Optom Vis Sci 84:689–704

Massof RW (2013) A general theoretical framework for interpreting patient-reported outcomes estimated from ordinally scaled item responses. Stat Methods Med Res. Feb 19. [Epub ahead of print] doi:10.1177/0962280213476380

Massof RW, Dagnelie G, Deremeik JT, DeRose JL, Alibhai SS, Glasner NM (1995) Low vision rehabilitation in the U.S. health care system. J Vis Rehabil 9:3–31 [Massof RW, Lidoff L (eds) (2001) Reprinted in low vision rehabilitation: service delivery, policy, and funding. AFB Press, New York, pp 267–306]

Massof RW, Hsu CT, Baker FH, Barnett GD, Park WL, Deremeik JT, Rainey C, Epstein C (2005a) Visual disability variables. I. The importance and difficulty of activity goals for a sample of low vision patients. Arch Phys Med Rehabil 86:946–953

Massof RW, Hsu CT, Baker FH, Barnett GD, Park WL, Deremeik JT, Rainey C, Epstein C (2005b) Visual disability variables. II. The difficulty of tasks for a sample of low vision patients. Arch Phys Med Rehabil 86:954–967

Massof RW, Deremeik JT, Park WL, Grover LL (2007a) Self-reported importance and difficulty of driving in a low vision clinic population. Invest Ophthalmol Vis Sci 48:4955–4962

Massof RW, Ahmadian L, Grover LL, Deremeik JT, Goldstein JE, Rainey C, Epstein C, Barnett GD (2007b) The Activity Inventory (AI): an adaptive visual function questionnaire. Optom Vis Sci 84:763–774

Matt AI, Pesudovs K, Daly A, Brown M, Chen CS (2011) Access to low vision rehabilitation services: barriers and enablers. Clin Exp Optom 94:181–186

McCabe P, Nason F, Demers-Turco P et al (2000) Evaluating the effectiveness of a vision rehabilitation intervention using an objective and subjective measure of functional performance. Ophthalmic Epidemiol 7: 259–270

Medicare benefits policy manual (2011) Chapter 7, CMS http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS012673.html; accessed May 2, 2013.

Morse AR, Massof RW, Cole RG, Mogk LG, O'Hearn AM, Hsu YP, Faye EE, Wainapel SF, Jackson ML (2010) Medicare coverage for vision assistive equipment. Arch Ophthalmol 128:1350–1357

Nowakowski RW (1994) Primary low vision care. Appleton and Lange, Norwalk

O'Connor PM, Lamoureux EL, Keeffe JE (2008) Predicting the need for low vision rehabilitation services. Br J Ophthalmol 92:252–255

Ochs AL, Newberry J, Lenhardt M, Harkins SW (1985) Neural and vestibular aging associated with falls. In: Birren JE, Schaie KW (eds) Handbook of the psychology of aging, 2nd edn. Van Nostrand Reinhold, New York

Owsley C, McGwin G, Sloane ME et al (2001) Timed instrumental activities of daily living tasks: relationship to visual function in older adults. Optom Vis Sci 78:350–359

Owsley C, McGwinn G Jr, Lee PP, Wasserman N, Searcey K (2009) Characteristics of low vision rehabilitation services in the United States. Arch Ophthalmol 127: 681–689

Park S, Fisher AG, Velozo CA (1994) Using the assessment of motor and process skills to compare occupational performance between clinic and home settings. Am J Occup Ther 48:697–709

Patel H, Turano KA, Broman AT, Bandeen-Roche K, Munoz B, West SK (2006) Measures of visual function and percentage of preferred walking speed in older adults: the Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci 47:65–71

Pedula KL, Coleman AL, Hillier TA, Ensrud KE, Nevitt MC, Hochberg MC, Mangione CM (2006) Visual acuity, contrast sensitivity, and mortality in older women: study of osteoporotic fractures. J Am Geriatr Soc 54:1871–1877

Pearce E, Crossland MD, Rubin GS (2011) The efficacy of low vision device training in a hospital-based low vision clinic. Br J Ophthalmol 95:105–108

Ramsey VK, Blasch BB, Kita A (2003) Effects of mobility training on gait and balance. J Vis Impair Blind 97:720–726

Reeves BC, Harper RA, Russell WB (2004) Enhanced low vision rehabilitation for people with age related macular degeneration: a randomized controlled trial. Br J Ophthalmol 88:1443–1449

Riddering A (2008) Evaluation and intervention for deficits in home and community mobility. In: Warren M (ed) Low vision: occupational therapy evaluation and intervention with the older adult. Revised edition. American Occupational Therapy Association, Bethesda, pp 131–157

Rovner BW, Casten RJ, Hegel MT, Massof RW, Leiby BE, Tasman WS (2011) Improving function in age-related macular degeneration: design and methods of a randomized clinical trial. Contemp Clin Trials 32:196–203

Safety of Seniors Act of 2007, Public Law 110–202. Web access: http://thomas.loc.gov/cgi-bin/bdquery/z?d110:SN00845:@@@L&summ2=m&. Accessed 23 Apr 2008

Salive ME, Guralnik J, Glynn RJ, Christen W, Wallace RB, Ostfield AM (1994) Association of visual impairment with mobility and physical function. J Am Geriatr Soc 42:287–292

Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE (2008) Fear of falling: measurement

strategy, prevalence, risk factors and consequences among older persons. Age Ageing 37:19–24
Scott I, Smiddy W, Schiffman J et al (1999) Quality of life of patients with low vision and the impact of low-vision services. Am J Ophthalmol 128:54–62
Skinner HB, Barrack RL, Cook SD (1984) Age-related decline in proprioception. Clin Orthop Relat Res 184:208–211
Smith HJ, Dickinson CM, Cacho I et al (2005) A randomized controlled trial to determine the effectiveness of prism spectacles for patients with age-related macular degeneration. Arch Ophthalmol 123:1042–1050
Soong GP, Lovie-Kitchin JE, Brown B (2001) Does mobility performance of visually impaired adults improve immediately after orientation and mobility training? Optom Vis Sci 78:657–666
Spaulding SJ, Patla AE, Elliott DB, Flanagan J, Rietdyk S, Brown S (1994) Waterloo vision and mobility study: gait adaptations to altered surfaces in individuals with age-related maculopathy. Optom Vis Sci 71:770–777
Stelmack JA, Szlyk JP, Stelmack TR et al (2006) Measuring outcomes of low vision rehabilitation with the Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ-48). Invest Ophthalmol Vis Sci 47:3253–3261
Stelmack JA, Tang C, Reda DJ et al (2008a) Outcomes of the Veterans Affairs Low Vision Intervention Trial (LOVIT). Arch Ophthalmol 126:608–617
Stelmack JA, Rinne S, Mancil RM, Dean D, Moran D, Tang XC, Cummings R, Massof RW (2008b) Successful outcomes from a structured curriculum used in the Veterans Affairs Low Vision Intervention Trial. J Vis Impair Blind 102:636–648
Stemack JA, Szlyk JP, Stelmack TR, Demers-Turco P, Williams RT, Moran D, Massof RW (2004) Psychometric properties of the Veterans Affairs Low-Vision Visual Functioning Questionnaire. Invest Ophthalmol Vis Sci 45:3919–3928
Straw LB, Harley RK (1991) Assessment and training in orientation and mobility for older persons: program developing and testing. J Vis Impair Blind 85:291–296
Straw LB, Harley RK, Zimmermann GJ (1991) A program in orientation and mobility for visually impaired persons over age 60. J Vis Impair Blind 85:108–113
Tabrett DR, Latham K (2011) Factors influencing self-reported vision-related activity limitations in the visually impaired. Invest Ophthalmol Vis Sci 52:5293–5302
Tinetti ME, Mendes de-Leon CF, Doucette JT, Baker DI (1994) Fear of falling and fall-related efficacy in relationship to functioning among community-living elders. J Gerontol 49:M140–M147
Tobis JS, Block M, Steinhaus-Donham C, Reinsch S, Tamaru K, Weil D (1990) Falling among the sensorially impaired elderly. Arch Phys Med Rehabil 71:144–147
Turano KA, Dagnelie G, Herdman SJ (1996) Visual stabilization of posture in persons with central visual field loss. Invest Ophthalmol Vis Sci 37:1483–1491
Turano KA, Massof RW, Quigley HA (2002) A self-assessment instrument designed for measuring independent mobility in RP patients: generalizability to glaucoma patients. Invest Ophthalmol Vis Sci 43:2874–2881
Turano KA, Broman AT, Bandeen-Roche K et al (2004) Association of visual field loss and mobility performance in older adults: Salisbury Eye Evaluation Study. Optom Vis Sci 81:298–307
U.S. National Institutes of Health (2006) Feasibility study of a chronic retinal stimulator in retinitis pigmentosa. ClinicalTrials.gov. ID NCT00279500, http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c07.pdf. Accessed on Mar 18, 2013
U.S. National Institutes of Health (2009) Low vision depression prevention trial for age related macular degeneration (VITAL). ClinicalTrials.gov. ID NCT00769015, http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c07.pdf. Accessed on Mar 18, 2013
Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ (1997) Fear of falling and restriction of mobility in elders. Age Ageing 26:189–193
Vigili G, Rubin G (2003) Orientation and mobility training for adults with low vision. Cochrane Database Syst Rev (4):CD003925
Wald HW, Oswald F, Zimprich D (1999) Everyday competence in visually impaired older adults: a case for person-environment perspectives. Gerontologist 39:140–149
Walter C, Althouse R, Humble H, Smith W, Odom JV (2007) Vision rehabilitation: recipient's perceived efficacy of rehabilitation. Ophthalmic Epidemiol 14: 103–111
Warren M (ed) (2008) Low vision: occupational therapy evaluation and intervention with the older adult. Revised edition. American Occupational Therapy Association, Bethesda
Watson GR (2001) Low vision in the geriatric population: rehabilitation and management. J Am Geriatr Soc 49:317–330
Watson GR, Wright V (1996) A low vision reading comprehension test. J Vis Impair Blind 90:486–494
West SK, Rubin GS, Broman AT, Munoz B, Bandeen-Roche K, Turano K (2002) How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. Arch Ophthalmol 120:774–780
Wiener WR, Siffermann E (2010) The history and progression of the profession of O&M. In: Wiener W, Welsh R, Blasch B (eds) Foundation of orientation and mobility, vol I. American Foundation for the Blind, New York
Wolffsohn JS, Cochrane AL (2000) Design of the low vision quality-of-life questionnaire (LVQOL) and measuring the outcome of low vision rehabilitation. Am J Ophthalmol 130:793–802

# Index



H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5, © Springer-Verlag Berlin Heidelberg 2013