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Review Article

Age-Related Macular Degeneration: Alternative Therapy

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Abstract

Age-related macular degeneration (AMD) is a major cause of blindness worldwide. Currently, 1.75 million people are affected by advanced AMD, and with ageing population 3 million people will be affected by 2020 in many countries. At present, 7 million people are at risk of developing advanced AMD, and 1 in 3 persons aged 70 or older with early AMD will develop advanced disease over 10 years. The devastating impact to both the individual and general public is staggering. No effective preventive drug therapies exist although nutritional and behavioral modifications can reduce progression to advanced age-related macular degeneration. Application of vascular endothelial growth factor inhibitors through intraocular injections represents a treatment option only for selected types of AMD and is related with short-term efficacy, required re-treatments and ocular and systemic side effects. There is a need for new drugs taken in a non-invasive way. A growing body of the literature indicates the involvement of lipids and lipoproteins in the formation of AMD lesions. The most commonly used lipid lowering drugs are statins with a strong efficacy record in reducing cholesterol. The goal of this review is to evaluate the effectiveness of these drugs as an alternative therapy in AMD. Improving treatments that reverse, prevent, or even delay the onset of AMD would have significant benefit to both the individual and society.

Keywords: Age-related macular degeneration, Lipoproteins, Non-invasive treatment, Lipid lowering drugs

1. Introduction

Age-related macular degeneration (AMD) is a major cause of blindness worldwide (Evans, (2001). Currently, 1.75 million people are affected by advanced AMD, and with ageing population 3 million people will be affected by 2020 in many countries. At present, 7 million people are at risk of developing advanced AMD, and 1 in 3 persons aged 70 or older with early AMD will develop advanced disease over 10 years (Mukesh et al., 2004). The devastating impact to both the individual and general public is staggering. In Canada and Australia, the financial impact is estimated to be $2.6 billion on the gross domestic product (Brown et al., 2005; Centre of Eye Research Australia, 2006). The continued trend for increased life expectancy predicts a doubling in the number of people with AMD with costs reaching $59 billion over the next 20 years (Centre of Eye Research Australia). Since 2000, the number of people age 50 and older with late age-related macular degeneration (AMD) has climbed by 25 percent, to 2,069,403.This startling increase was documented in "Vision Problems in the U.S.," a report released by Prevent Blindness America and the National Eye Institute and compiled by researchers from Johns Hopkins University.

Improving treatments that reverse, prevent, or even delay the onset of AMD would have significant benefit to both the individual and society.

Age-related macular degeneration is typically classified into two clinical forms, no exudative or “dry” and exudative or “wet”, both of which can lead to visual loss. In the dry or no exudative form, visual loss is usually gradual. The hallmark changes that are seen in the macula are yellow subretinal deposits called drusen, or retinal pigment epithelium (RPE) hyperpigmentary or hypopigmentary irregularities. Drusen may enlarge and become confluent, and even evolve into drusenoid RPE detachments, where the RPE becomes separated from its underlying Bruch’s membrane. These drusenoid detachments often progress to geographic atrophy, where the RPE dies from apoptosis or into wet AMD. In the wet form, also called

exudative or neovascular AMD, vision loss can occur suddenly when a choroidal neovascular membrane develops in the sub-RPE, between the RPE and Bruch's membrane, and it subretinal space, between the neurosensory retina and RPE, and it leaks fluid or blood (Ryan, 2006). Major risk factors include cigarette smoking, nutritional factors, cardiovascular diseases, and genetic markers, including genes regulating complement, lipid, angiogenic, and extracellular matrix pathways (Lim et al., 2012).

No effective preventive drug therapies exist although nutritional and behavioral modifications can reduce progression to advanced age-related macular degeneration. Current treatment options by endothelial growth factor (VEGF) inhibitors – anti-VEGF therapy are limited to the late stage of the disease, when central vision is already under great threat, and even new treatments make little impact on the rate of blindness. Monthly intravitreal anti-VEGF injections with systemic exposure to anti-VEGF will be replaced by new drugs taken in a non-invasive way. There is no effective treatment for AMD or for arresting its progression in its earliest phases.

Overlapping in risk factors for AMD and cardiovascular disease had led some to suggest that the pathophysiology of these diseases have similar causal pathways (Snow and Seddon, (1999)). Positive associations between AMD and cardiovascular risk factors lend support to this proportion (blood pressure, plasma cholesterol, and smoking) (Evans, (2001)). The prominent histopathological and clinical lesions in AMD involve Bruch's membrane, a specialized vascular intima separating the photoreceptors and their support cells, the retinal pigment epithelium (RPE), from their blood supply. Because these lesions and Bruch's membrane contain abundant lipids, including cholesterol (Haimovici et al., (2001), Curcio et al., (2001)), it is possible that AMD and cardiovascular disease share common mechanisms at the level of the vessel wall.

The latest findings (Ebrahimi and Handa, 2011; Charters, 2013) indicates that AMD is a multifactorial disease of the photoreceptor support system, the retinal pigment epithelium (RPE), and Bruch's membrane in the choroid with involvement of lipids and lipoproteins in the formation of AMD lesions. Dr. Curcio proposed a unified theory of AMD pathogenesis based on lipid deposition at Retina Subspecialty Day during the American Academy of Ophthalmology annual meeting in Chicago (June,2012). The theory hypothesizes that oil red O binding in Bruch's membrane, which is the single biggest aging change in normal eyes, serves as a barrier to delivery of micronutrients to the RPE and photoreceptors and may be a source of lipids that can be peroxidized by free radicals into proinflammatory, proangiogenic, and cytotoxic compounds. This provides a cleavage plane for neovessels from the choroid growing under the RPE. This lipid deposition in Bruch's membrane may be a manifestation of the systemic process of perifibrous lipid deposition and the foundation for atherosclerosis, xanthoma, and lipid keratopathy, she explained. Lipids are the biggest component of drusen, especially soft drusen, and are dominated by esterified cholesterol (oil red O). Lipoprotein particles accumulate in Bruch's membrane with aging and form basolinear deposits. The RPE secretes apoB and E particles that are retained in Bruch's membrane; the RPE expresses hallmark genes of a lipoprotein secretor and the apolipoproteins are localized to drusen. The lipoproteins come from multiple lipid sources; in Bruch's membrane, the lipoprotein fatty acids resemble those from dietary sources. There are now new precursors with potential for clinical intervention, including lipoprotein metabolism and modification and regulation of inflammation. This means that new treatments for pharmaceutical and dietary modulation of dyslipidemia can be retooled to restore Bruch's membrane.

The most commonly used lipid lowering drugs are statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Recent experimental evidence suggests that these agents appear to display additional cholesterol independent or pleiotropic effects, contributing to prevention and inhibition of atherosclerosis. The statins' vascular pleiotropic effects include improvement of endothelial function, slowing the inflammation process, inhibition of the thrombus formation, enhancement of plaque stability and decreasing oxidative stress (Wolfovitz, (2005)).

Statins are widely used in clinical practice because, they are effective and evidence based drugs. The Heart Protection Study randomized more than 20,000 patients, and the value of statins in reducing adverse cardiovascular events in high–risk patients, including the elderly, women, and even in those with low cholesterol levels was beyond doubt (Li, (2005)). As a result, statins are now considered as one of the most

powerful classes of agents for the treatment of vascular disease (Li, (2003), Ostadal, (2003)). Statins have a strong efficacy record in reducing cholesterol, cardiovascular events, and (in secondary prevention for men under age 70, deaths (Baigent et al., 2005; Golomb et al., 2009; Egan and Colman, 2011).

Statins are rapidly becoming frontline therapy among patients with diabetes mellitus, hypertension, and other known vascular risk factors. Statins lower serum lipid levels, and accumulation of lipids in the Bruch membrane and drusen is a key pathophysiologic pathway for AMD development (Guymer et al., 2005). Statins also appear to have beneficial effects on other AMD pathways such as oxidative damage and inflammation (Guymer et al., 2005, 2008). Choroidal neovascular membranes associated with ARMD include macrophages (Grossniklaus, 2000), which may respond to statins. The goal of this review is to evaluate the effectiveness of these drugs as an alternative therapy in AMD.

The National Centre for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM) was searched using the terms "Statins in age-related macular degeneration".

2. Statins and incidence of age-related macular degeneration

The association between the use of statins and age-related macular degeneration has been evaluated in many clinical studies; however the results have been contradictory. Klein et al. (2001) have an evaluated the impact of "lipid lowering agents" and Delcourt et al (2001) evaluated "hypocholesterolaemic" drugs and found no association with early AMD or late AMD. Thus the aggregation of statin and non-statin medications, as was probably done in these studies, would bias any association towards the null.

Smeeth et al. (2005) conducted a population based case control study. Case group consists of 18007 people with diagnosed ARMD and control group of 86169 people respectively matched on age, sex, and general practice. The crude odds ratio for the association between any recorded exposure to statins and ARMD was 1.32 (95% CI 1.17 to 1.48), but this reduced to 0.93 (95% CI 0.81 to 1.07, p=0.33) after adjustment for consultation rate, smoking, alcohol intake, body mass index, atherosclerotic disease, hyperlipidaemia, heart failure, diabetes mellitus, hypertension, use of other cardiovascular drugs, and use of fibrates. The authors stated that there was no evidence that the risk varied by dose of statin, duration of use, or that the risk varied for individual statins and concluded that in the short and medium term statin use is not associated with a decreased risk of AMD, and whether subgroups of patients with specific forms of AMD (particularly choroidal neovascularisation) benefit from statin therapy remains a possibility.

Klein et al. (2007) in the observational analysis of a randomized clinical trial have found that, use of statins was not associated with AMD. This study was limited to older females and the results should only be considered generalisable to females aged 63 and older. McGwin et al. (2006) evaluated both the use of cholesterol-lowering medications as a group and the use of statins specifically with regard to the risk of AMD. A case-control study was conducted using data from the Cardiovascular Health Study, a population-based prospective study of adults enrolled in 1989 and 1990. The authors stated that no association exists between having used cholesterol-lowering medications and AMD. However, there was a suggestion that statin use might increase the risk of AMD. The results of this study should be interpreted in light of its limitations. Firstly, subjects with ARMD were not identified and not confirmed by a standardized comprehensive eye examination and the grading of fundus photographs. This limitation prohibits analyses with respect to disease severity and type. Also, without confirmatory diagnostic information, there is also the possibility of misclassification with respect to AMD status. Secondly, this study aggregated statins and non-statins into the group of cholesterol-lowering medications.

Data from large population-based studies, including previous analyses from the Blue Mountains and Beaver Dam studies, have not found a protective association between statin use and AMD (Klein et al., (2003); van Leeuwen et al., (2004)), Kaiserman et al. (2009) also stated that statin use is not reducing the risk for wet ARMD. Absence of evidence is not evidence of absence. In another new analysis using data from the Beaver Dam Eye Study in Wisconsin, statin use at the 10-year examination was not associated with the subsequent incidence of early or late AMD, or progression of AMD at the 15-year examination (Klein et al., (2007)). Data from new case-control study confirmed also that use of statins was not associated with newly diagnosed exudative AMD. The study had 80% statistical power to detect a protective effect of 0.70, but it cannot exclude a smaller effect.

Chuo et al. (2007) evaluated the effect of lipid-lowering agents in the development of AMD through a meta-analysis of observational studies, estimating the pooled relative risk (RR) for all eight studies, and also for seven studies examining the use of statins, for those RR was 0.70 (95% CI, 0.48-1.03). The authors concluded that lipid-lowering agents, including statins, do not appear to lower the risk of developing AMD, although clinically significant effects cannot be excluded. Hall et al. (2001) reported a significantly lower frequency of AMD (defined broadly as all types and severities) among statin users relative to non-users. The OR reported in that study was 0.14, 95% CI 0.02-0.83. The limitations of the Hall et al. (2001) have been addressed in detail and include the small sample size and the cross sectional designs (van Leeuwen, (2001)). Martin-Du Pan RC (2003) confirmed that statins are well tolerated and they could reduce the risk of macular degeneration. Data from cohort study of patients with bilaterial large drusen within a multicenter, randomized, clinical trial are not consistent with a strong protective effect (risk ratio, $\leqslant$ 0.85) of statins on the development of advanced AMD among these patients (Maguire et al., (2009)).

Baghdasarian et al. (2004) in a cross-sectional analysis have found that AMD was less common among statin users than nonusers (4% [1/27] vs. 22% [76/352]; p=0.02). Etminan et al. (2008) in the observational study have found a slightly higher risk of developing AMD among statin users. Observational studies evaluating treatment effects are subject to range a biases, bringing to heterogeneity of findings. Drobek-Slowik et al., (2008) in case-control study revealed statin use may be a protective factor against AMD. Treatment indication and compliance biases, which refer to distortion of associations resulting from known and unknown differences in participant characteristics, prescribed the treatment and the treatment actually taken, are difficult to quantify and may also vary in magnitude between the studies. There is evidence that the pattern, prescription, and type of statin usage have changed in the last decade. Furthermore, there is evidence that not all statins are equally effective for lipid lowering. In a meta-analysis, atorvastatin displayed two to four times the potency of simvastatin in reducing total cholesterol levels (McCarty, (2001). Thus, it is likely that the type and dosage of evaluated statins are different. Statins could provide some protective effect that is too small to be measured by small studies.

In the latest largest study conducted by Shalev et al. (2011) investigating statin use and the risk of age related macular degeneration in large health organization in Israel the crude incidence rate of AMD among patients at the lowest quintile of persistence with statins (7.18 per 1,000) was comparable to that of highest persistence quintile (7.13 per 1,000). After adjustment for potential confounders, patients in the highest quintile of persistence with statins had a hazard ratio of 0.99 (95% Confidence interval: 0.78-1.26) for AMD compared with patients in the lowest proportion of days covered (PDC) quintile. In addition to age, AMD was found to associate with past smoking, asthma, diabetes and frequent visits to ophthalmologists or primary physicians prior to index date. The authors concluded and agreed with previous studies that showes no association berween persistent use of statins and reduced risk of ARMD. A Cochrane database review published in March 2012 also did not find sufficient evidence to determine the effectiveness and safety of statins for the prevention or delaying the progression of AMD (Gehlbach et al., 20120, since only two studies met the selection criteria. One trial reported insufficient details to assess the risk of bias; the other trial is ongoing.

Of the completed trial, the analyses of 30 participants did not show a statistically significant difference between the simvastatin and the placebo arm in visual acuity at three months of treatment (decimal visual acuity 0.21 ± 0.56 in simvastatin and 0.19 ± 0.40 in placebo arm) or 45 days after the completion of treatment (decimal visual acuity 0.20 ± 0.50 in simvastatin and 0.19 ± 0.48 in placebo arm). The lens and retina status were unchanged during and after the treatment period for both groups. In conclusion, statins could provide some protective effect that is too small to be measured by small studies, because at the same time but in a large prospective study including 38 192 men and 90 874 women during 12 years of follow-up Gao et al. (2012) have found that regular use of statins was associated with a modest reduction in Parkinson disease risk. Peponis et al. (2010) in a mini review also concluded that there is a need for large scale prospective studies with a long follow-up period and accurate assessment of AMD to further explore this matter.

In the latest study examined the role of heme oxygenase-1 as a target and potential mediator of statins in cultured human RPE cells Kim et al. (2012) suggested that simvastatin might have some clinical benefits in

preventing retinal diseases associated with oxidative stress, such as AMD.

3. Statins in the treatment of age-related macular degeneration

The beneficial effect achieved by the treatment of endothelial dysfunction in chronic cardiovascular diseases is already evidence belonging to the basic treatment of the disease. Given the fact that the vascular system is uniform and consubstantial both physiologically, pathophysiologically and in terms of therapy, and that it plays a key role in AMD, endothelial dysfunction should be treated (Fisher, (2008; 2009)).

McCarty et al. (2001) found that the self-reported use of cholesterol lowering medications was associated with a fourfold decreased risk of AMD progression in those who had AMD at baseline; however, because of small sample size this finding was not statistically significant. The reliance on self-reported information on statin use also represents a potential limitation of this study. McGwin et al. (2003) also reported a significant risk reduction for statin users (OR 0.30, 95% CI 0.20 - 0.45) and concluded that subjects with ARMD were significantly less likely to have filled a statin prescription. The results of this study should be interpreted in light of its strengths and limitations. The primary strength of this study is the use of the nested case-control design that allowed for the evaluation of statin use that occurred before AMD diagnosis. Given the size of the study base, this study was able to identify a large number of AMD cases (550) and matched controls (5500) thereby enhancing the statistical power of the study relative to other studies evaluating the relation between statin use and AMD. This study had information on actual filled prescriptions and did not rely on self-reported medication use, as have other studies. Although there is no information on whether the medications were actually taken, the succession of prescription refills during the observation periods among the majority of statin users suggests that these medications were actually being taken. Finally, this study population was limited to older males and the results should only be considered generalisable to males aged 50 and older.

McGwin et al. (2005), in the case-control study of 871 AMD cases and 11,717 controls after adjusting for the confounding influence of age, gender, and race, revealed a statistically significant relationship between AMD and use of cholesterol-lowering medications (OR, 0.79; 95% CI, 0.63-0.99). The results of this study add to the growing body of evidence that cholesterol-lowering medications may reduce the risk of developing AMD. In the latest analysis of the Blue Mountains Eye Study in Australia, while controlling for age and other factors, statin users at baseline and at the five-year follow-up had a 67% lowered risk of indistinct soft drusen, a key late AMD precursor lesion, at the 10-year examination. Statin use, however, as stated by authors, was not related to the incidence of late AMD or other early AMD signs (Tan et al., (2007). This large population-based study as an observational study evaluating treatment effects is subject to a range of biases which were discussed earlier.

Wilson et al. (2004) in a retrospective consecutive case series investigated the relationship between statin and aspirin use and the risk of choroidal neovascularization (CNV) in patients with AMD.

Age-related macular degeneration disease status and time of onset of CNV was compared between patients treated or not treated with statins for at least 6 month. Of CNV subjects, 20% used statins, compared with 38% of dry AMD subjects without geographic atrophy and 33% of controls with geographic atrophy (hazard ratio = 0.51, 95% confidence interval (CI) = 0.31-0.86, p=0.01). The general consensus is that therapy with statins or aspirin is significantly associated with decreased rates of CNV (Wilsonet al., (2004), Girgis, (2004), Gaynes, (2004)). The strength of this study (Wilson et al., (2004)) is the used of main outcome measure, represented by angiographically evident CNV, and also the diagnosis, which was based on review of fundus photographs and fluorescein angiograms in masked fashion. The latest experimental study conducted by Sagara et al. (2007), evaluated the effect of specific statin-pitavastatin on CNV in rats and has also advocated the use of pitavastatin in preventing CNV development in AMD patients, based on claims that the therapeutic dose of pitavastatin for human hypocholesterolemia effectively suppressed experimental CNV in rats. The authors reported that pitavastatin-treated rats had significantly less fluorescein leakage, evaluated by masked observers; reduced thickness of CNV and decreased gene expression of VEGF. These encouraging results should be confirmed in clinical trials.

Schmeer et al. (2007) have recently advocated the use of statins in retinal eye diseases, based on their anti-apoptotic, anti-proliferative effects, besides lipid-lowering and anti-inflammatory properties. The

authors presented evidence for the role of heat shock proteins (Hsps) as target of statin-mediated neuroprotective effects in ocular diseases.The general consensus is that a randomized trial of statin use in AMD patients is warranted (Klein et al., (2003), McGwin et al., (2003; 2005), Wilson et al., (2004), Chuo et al., (2007), Wong and Rogers, (2007)).

Wong and Rogers (2007) also advocated initiation of a randomized controlled trial. The authors estimated the required sample size, described clinically relevant endpoints, and concluded that only 1,704 participants are needed for a five-year trial to evaluate the effects of statins on slowing AMD

Progression by 25% or more (relative risks RR of 0.75 or lower), assuming a cumulative progression rate of 6% for the placebo group.

Gehlbach and Hatef (2009) evaluated the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and/or progression of AMD based on findings of randomized controlled trials (RCTs). The authors stated that evidence from currently available RCTs was insufficient to conclude that statins have any role in preventing or delaying the onset or progression of age-related macular degeneration.

4. Conclusion

In conclusion, there are potentially multiple biological bases for the protective effect of statins on the risk of AMD. With regard to the potential for a lipid lowering effect, cholesterol is a ubiquitous component of drusen in normal and AMD eyes. With regard to the potential for pleiotropic effects, many of the same processes that occur in the atherosclerotic intima, probably also occur in AMD. Neovascularisation is a major complication in both conditions. Therefore, angiogenesis is potential point of statin modulation. Taken into account that not all statins are equally effective, the challenge for future laboratory research will be to determine the best type and dosage of statins and also to determine which processes are modulated by statins in vivo and therefore are primarily responsible for the apparent beneficial effects observed in the previous studies. Clearly, further observational studies cannot adequately address many unanswered questions. It is time to conduct a randomized controlled trial to provide direct evidence of the effectiveness of specific type statin in lowering the incidence and progression of AMD. New intervention as statins usage to prevent the development of age-related macular degeneration and its progression remain an important strategy to limit the morbidity of this significant public health problem. Improving treatments that reverse, prevent, or even delay the onset of AMD would have significant benefit to both the individual and society.

References

Baghdasarian SB, Jneid H, Hoogwerf BJ (2004). Association of dyslipidemia and effects of statins on nonmacrovascular diseases. Clin Ther. 26(3): 337-351.

Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al. (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366: 1267–1278.

Brown MM, Brown GC, Stein JD, Roth Z, Campanella J, Beauchamp JR.(2005) Age-related macular degeneration: economic burden and value-based medicine analysis. Canadian Journal of Ophthalmology;40(3):277–287.

Centre of Eye Research Australia, Centrally Focused: The Impact of Age-Related Macular Degeneration, Access Economics, Melbourne, Australia, 2006.

Charters L. AMD pathogenesis based on lipid deposition may answer questions.(2013) Ophthalmology Times eReport.

Chuo JY, Wiens M, Etminan M, Maberley DA (2007). Use of lipid-lowering agents for the prevention of age-related macular degeneration: a meta-analysis of observational studies. Ophthalmic Epidemiol. 14(6): 367-374.

Curcio CA, Millican CL, Bailey T, Rudolf M (2001). Accumulation of cholesterol with age in human Bruch's membrane. Invest Ophthalmol Vis Sci. 42: 265-274.

Curcio CA. AMD pathogenesis based on lipid deposition . Retina Subspecialty Day American Academy of Ophthalmology annual meeting in Chicago, June 2012.

Delcourt C, Michel F, Colvez A, Leger CL, Michel F, Papoz L (2001). Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. Ophthalmic Epidemiol. 8: 237-249.

Drobek-Slowik M, Karczewics D, Safranow K, Jakubowska K, Chlubek DI (2008). Use of statins as a form of protection against macular degeneration (AMD). Klin Oczna, 110(1-3): 50-54.

Ebrahimi KB, Handa JT. Lipids, Lipoproteins, and Age-Related Macular Degeneration (2011). Journal of Lipids; Article ID 802059, doi:10.1155/2011/802059

Egan A, Colman E (2011) Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med 365: 285–287.

Etminan M, Brophy JM, Maberley D (2008). Use of statins and angiotensin converting enzyme inhibitors (ACE-is) and the risk of age-related degeneration: nested case-control study. Curr. Drug Saf. 3(1):24-26.

Evans J (2001). Risk factors for age-related macular degeneration. Prog Ret Eye Res. 20: 227-253.

Fischer T (2008). A new possible strategy of prevention and preventive treatment of age-related macular degeneration. Orv Hetil. 149(3): 121-127.

Fischer T (2009). A new possible strategy of prevention and preventive treatment of age-related macular degeneration resting on recent clinical and pathophysiological observations. Orv Hetil. 150(11):503-512.

Fong DS, Contreras R (2010). Recent statin use and 1-Year incidence of exudative age-related macular degeneration. Am J. Ophthalnol. 149(6): 955-958.

Gao X,. Simon KC, Schwarzschild MA., Ascherio A (2012) Prospective Study of Statin Use and Risk of Parkinson Disease. Arch Neurol. 2012;69(3):380-384.

Gaynes BI (2004). Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among age-related macular degeneration patients. Am J Ophthalmol. 138(6): 1089.

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

Gehlbach P, Li T, Hatef E (2012). Cochrane Eyes and Vision Group. ed. "Statins for age-related macular degeneration". Cochrane Database Syst Rev 3: CD006927. doi:10.1002/14651858.CD006927.pub3. PMID 22419318.

Girgis RA, McKee HD (2004). Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration. Am J

Ophthalmol. 138(4): 697.

Golomb BA, Parrish J, Broadwin JA (2009) Statins and mortality. On the Risk 25: 66–71.

Grossniklaus HE, Cingle KA, Yoon YD (2000). Correlation of histologic 2-dimensional reconstructional and confocal scanning laser microscopic imaging of choroidal neovascularization in eyes with age-related maculopathy. Arch Ophthalmol. 118: 625-629.

Guymer RH, Chiu AW, Lim L, Lim LL, Baird PN, et al. (2005). HMG CoA reductase inhibitors (statins): do they have a role in age-related macular degeneration? Surv Ophthalmol; 50(2): 194-206.

Guymer RH, Dimitrov PN, Varsamidis M, Lim LL, Baird PN, et al (2008). Can HMG Co-A reductase inhibitors (statins) slow the progression of age-related macular degeneration? The age-related maculopathy statin study (ARMSS). Clin. Interv. Aging. 3(3):581-593.

Haimovici R, Gantz DL, Rumelt S, et al. (2001). The lipid composition of drusen, Bruch's membrane, and sclera by hot stage polarizing microscopy. Invest Ophthalmol Vis Sci. 42: 1592-1599.

Hall NF, Gale CR, Syddall H, Phillips DI, Martyn CN (2001). Risk of macular degeneration in users of statins: cross sectional study. BMJ. 323(7309): 375-376.

Kaiserman N, Vinker S, Kaiserman I. (2009). Statins do not decrease the risk for wet age-related macular degeneration. Curr.Eye Res. 34(4): 304-310.

Kim KJ, Kim KS, Kim NR, Chin HS.(2012) Effects of Simvastatin on the expression of Heme Oxygenase-1 in Human Retinal Pigment Epithelial Cells. Invest Ophthalmol Vis Sci. 21;53(10):6456-6464.

Klein R, Deng Y, Klein BE (2007). Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: Women's Health Initiative Sight Exam ancillary study. Am J Ophthalmol . 43(3): 473-483.

Klein R, Klein BE, Jensen SC, Cruickshanks KJ, Lee KE, et al (2001). Medication use and the 5-year incidence of early age-related maculopathy. Arch Ophthalmol. 119: 1354-1359.

Klein R, Klein BE, Tomany SC (2003). Relation of statin use to the 5-year incidence and progression of age-related maculopathy. Arch Ophthalmol. 121(8): 1151-1155.

Klein R, Knudston MD, Klein BE (2007). Statin use and the live-year incidence and progression of age-related macular degeneration. Am.J.Ophthalmol. 144(1):1-6.

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

Leeuwen RV, Tomany SC, Wang JJ (2004). Is medication use associated with the incidence of early age-related maculopathy? Pooled findings from 3 continents. Ophthalmol. 111:1169-1175.

Li JJ (2003). Rapid effects on lipid profile and C-reactive protein by simvastatin in patients with hypercholesterolemia. Clin Cardiol. 26: 472-476.

Li JJ, Hu SS (2005). Early, Intensive and long-term statin therapy in acute coronary syndrome: focus on anti-inflammatory mechanisms. Vascular Disease Prevention. 2(3): 181-186.

Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. (2012) Age-related macular degeneration. The Lancet, 379, Issue 9827, 1728 – 1738.

Maquire MG, Ying GS, McCannel CA, Lin C, Dai Y (2009). Statin use and the incidence of advanced age-related macular degeneration in the complications of age-related macular degeneration prevention trial (CAPT). Ophthalmology. 138(5):698-704.

Martin-Du Pan RC (2003). Prevention of cardiovascular and degenerative diseases: I. Aspirin, statins, or vitamins? Rev Med Suisse Romande. 123(3): 175-181.

Mc Carty CA, Mukesh BN, Guymer RH (2001). Cholesterol-lowering medications reduce the risk of age-related maculopathy progression. MJA. 175: 340.

McGwin G Jr, Owsley C, Curcio CA, Crain RJ (2003). The association between statin use and age related maculopathy. Br J Ophthalmol. 87(9): 1121-1125.

McGwin Jr G, Xie A, Owsley C (2005). The use of cholesterol-lowering medications and age-related macular degeneration. Ophthalmol. 112(3): 488-494.

McGwin JrG, Modjarrad K, Hall TA (2006). 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the presence of age-related macular degeneration in the Cardiovascular Health Study. Arch Ophthalmol. 124(1): 33-37.

Mukesh BN, Dimitrov PN, Leikin S. (2004) Five-year incidence of age-related maculopathy: the visual impairment project," Ophthalmology, 111(6), 1176–1182.

Ostadal P, Alan D, Hajek P (2003). The effect of early treatment by cerivastatin on the serum level of C-reactive protein, interleukin-6, and interleukin-8 in the patients with unstable angina and non-Q-wave myocardial infarction. Mol Cell Biochem. 246: 45-50.

Peponis V, Chalkiadakis SE, Bonovas S, Sitaras NM.(2010) The controversy over the association between statins use and progression of age-related macular degeneration: a mini review. Clinical Ophthalmology,4 ;865 – 869.DOI: http://dx.doi.org/10.2147/OPTH.S12869

Prevent Blindness America and the National Eye Institute report "Vision Problems in the U.S", 2012.

Ryan S, Retina, vol. 1, Elsevier Health Sciences, 4th edition, 2006

Sagara N, Kawaji T, Takano A (2007). Effect of pitavastatin on experimental choroidal neovascularization in rats. Exp Eye Res. 84(6): 1074-1080.

Schmeer C, Kretz A, Isenmann S (2007). Therapeutic potential of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for the treatment of retinal and eye diseases. CNS Neurol. Disord Drug Targets. 6(4): 282-287.

Shalev V, Sror M, Goldshtein I, Kokia E, Chodick G (2011). Statin use and the risk of age related macular degeneration in a large health organization in Israel. Ophthalmic Epidemiol.18(2):83-90

Smeeth L, Cook C, Chakravarthy U, Hubbard R, Fletcher AE (2005). A case control study of age related macular degeneration and use of statins. Br J Ophthalmol . 89(9): 1171-1175.

Snow KK, Seddon JM (1999). Do age-related macular degeneration and cardiovascular disease share common antecedents? Ophthalmic Epidemiol. 6: 125-143.

Tan JS, Mitchell P, Rochtchina E, Wang JJ (2070). Statins and the long-term risk of incident age-related macular degeneration: the Blue Mountains Eye Study. Am J Ophthalmol: 143(4): 685-687.

Wilson HL, Schwartz DM, Bhatt HR (2004). Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration. Am J Ophthalmol. 137(4): 615-624.

Wolfovitz E (2005). The pleiotropic effects of statins. Harefuah; 144(8): 577-582, 597.

Wong TY, Rogers SL (2007). Statins and age-related macular degeneration: time for a randomized controlled trial? Am J Ophthalmol. 144(1): 117-119.

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