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*Review*

# HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors: Evaluation of the role and actions in age-related macular degeneration

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**Age-related macular degeneration (ARM) is a progressive late onset disease affecting central vision. It is the leading cause of irreversible blindness among older adults in developed countries, and with the aging population, the problem is increasing. 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. 3–hydroxy–3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, generically termed statins are the most commonly used lipid lowering drugs. The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that HMG CoA reductase inhibitors may be useful in the prevention and the treatment of age-related macular degeneration**

**Key words:** Atherosclerosis, age-related macular degeneration, pathophysiology, HMG CoA reductase inhibitors, pleiotropic effects.

## INTRODUCTION

Age-related macular degeneration (ARM) is a progressive late onset disease affecting central vision. It is the leading cause of irreversible blindness among older adults in developed countries, and with the aging population, the problem is increasing.

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 ARM or for arresting its progression in its earliest phases. Epidemiologic, genetic, and pathological evidence continues to accumulate, suggesting a possible link between risk factors for cardiovascular disease and age-related macular degeneration.

To overlap in risk factors for ARM and cardiovascular disease had led some to suggest that the pathophysiology of these diseases have similar causal path ways (Snow and Seddon, (1999)). Positive associations between ARM and cardiovascular risk factors lend support to this proportion (blood pressure, plasma cholesterol, smoking) (Evans, 2001). The prominent histopathological and clinical lesions in ARM 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 ARM and cardiovascular disease share common mechanisms at the level of the vessel wall.

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, generically termed statins are the most commonly used lipid lowering drugs. 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 cardio-vascular events in high–risk patients, including the elderly, women, and even in those with low cholesterol levels was beyond doubt (Li and Hu, 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 et al., 2003). Statins are rapidly becoming frontline therapy for 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 patho-physiologic 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 ARM include macrophages (Grossniklaus et al., 2000), which may respond to statins.

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that statins may be useful in the prevention and the treatment of age-related macular degeneration.

## 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 ARM or late ARM. The findings of these two studies may not be surprising if non-statin lipid lowering medications were more weakly associated with ARM.

Thus, the aggregation of statin and non-statin medi-cations, 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 AMD 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 AMD was 1.32 (95% CI 1.17 - 1.48), but this reduced to 0.93 (95% CI 0.81 - 1.07, p = 0.33) after adjustment for consultation rate, smoking, alcohol intake, body mass index, atherosclerotic disease, hyperlipidaemia, heart failure, diabetes mellitus, hyper-tension, 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 (parti-cularly choroidal neovascularisation) benefit from statin therapy remains a possibility.

Klein et al., (2007) in the observational analysis of a randomized clinical trial has 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 ARM were not identified and not confirmed by a standardized compre-hensive 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 ARM 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; Leeuwen et al., 2004). Kaiserman et al., (2009) also stated that statin use is not reducing the risk for wet AMD.

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).

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 ARM (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 design (Leeuwen, 2001). Martin-Du Pan RC (2003) confirmed that statins are well tolerated and they could reduce the risk of macular degeneration.

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 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 et al., 2001).

Thus, it is likely that the type and dosage of evaluated statins are different.

## 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 an 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 four fold decreased risk of ARM progression in those who had ARM 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 ARM 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 ARM diagnosis. Given the size of the study base, this study was able to identify a large number of ARM 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 ARM.

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 con-founding 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 (Wilson et 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 have also advocated the use of pitavastatin in preventing CNV development in AMD patients, based on claims that the therapeutic dose of pitavastatin for human hypochole-

sterolemia 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 disease, 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 end-points, 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.

## CONCLUSION

In conclusion, there are potentially multiple biological bases for the protective effect of statins on the risk of ARM.

With regard to the potential for a lipid lowering effect, cholesterol is a ubiquitous component of drusen in normal and ARM eyes.

With regard to the potential for pleiotropic effects, many of the same processes that occur in the atherosclerotic intima, probably also occur in ARM. 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 ARM.

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.

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