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Statins for age-related macular degeneration

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Abstract

Background—Age-related macular degeneration (AMD) is a progressive late onset disorder of the macula affecting central vision. Age-related macular degeneration is the leading cause of blindness in people over 65 years in industrialized countries (Congdon 2003). Recent epidemiologic, genetic and pathological evidence has shown AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD.

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*Indicates the major publication for the study

Declarations of Interest: None known.

Differences between Protocol and Review: The new risk of bias table has been included in this review. The WHO International Clinical Trials Registry Platform (ICTRP) was additionally searched.

Contributions of Authors: Conceiving the review: PG, TL

Designing the review: PG, TL

Co-ordinating the review: TL

Data collection for the review

Designing electronic search strategies: CEVG Trials Search Co-ordinator

Undertaking electronic searches: CEVG Trials Search Co-ordinator

Screening search results: PG, TL, EH

Organizing retrieval of papers: TL

Screening retrieved papers against inclusion criteria: PG, TL, EH

Appraising quality of papers: PG, TL, EH

Extracting data from papers: PG, TL, EH

Writing to authors of papers for additional information: TL

Providing additional data about papers: PG

Obtaining and screening data on unpublished studies: TL

Data management for the review

Entering data into RevMan: TL

Analysis of data: PG, TL, EH

Interpretation of data

Providing a methodological perspective: TL, EH

Providing a clinical perspective: PG, EH

Providing a policy perspective: PG, EH

Providing a consumer perspective: PG, EH

Writing the review: PG, TL, EH

Providing general advice on the review: PG, EH

Securing funding for the review: TL

Performing previous work that was the foundation of the current study: PG, TL, EH

Objectives—To examine the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and/or progression of AMD.

Search strategy—We searched CENTRAL in *The Cochrane Library*, MEDLINE, EMBASE and LILACS on 30 April 2009 and the WHO International Clinical Trials Registry Platform on 11 May 2009. We searched reference lists and the Science Citation Index. There were no language or date restrictions in the search for trials.

Selection criteria—We included randomized controlled trials (RCTs) that compared statins with other treatments, no treatment, or placebo in participants who were either susceptible to or diagnosed as having early stages of AMD.

Data collection and analysis—Two authors independently evaluated the search results against the selection criteria. Two Italian speaking colleagues extracted data. One author entered data. We did not perform a meta-analysis because only one completed RCT was identified.

Main results—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.

Of the ongoing trial, the preliminary analyses of 42 participants who completed 12 months follow-up did not show a statistically significant difference between the simvastatin and the placebo arm in visual acuity, drusen score or visual function (effect estimates and confidence intervals were not available). We contacted the investigators and will update the review as data become available.

Authors' conclusions—Evidence from currently available RCTs was insufficient to conclude that statins have any role in preventing or delaying the onset or progression of AMD.

Medical Subject Headings (MeSH)

Hydroxymethylglutaryl-CoA Reductase Inhibitors [*therapeutic use]; Macular Degeneration [*prevention & control]; Randomized Controlled Trials as Topic; Simvastatin [*therapeutic use]

MeSH check words

Humans

Background

Introduction

Age-related macular degeneration (AMD) is a progressive late onset disorder of the macula that affects central vision. Although AMD is the leading cause of blindness in people over 65 years in industrialized countries (Congdon 2003), its pathogenesis is not clearly

understood. It is believed that both genetic and environmental factors play a significant role in the development of the disease.

Epidemiology

The prevalence, incidence, and progression of AMD increase with age. Prevalence of any AMD (referred to as age-related maculopathy) in the Beaver Dam Eye Study was less than 10% in persons age 43 to 54 years, but more than tripled for persons age 75 to 85 years (AAO 2006; Klein 1992; Klein 2001). Joint data from the United States, Netherlands and Australia indicate the prevalence for late AMD is 0.2% in the 55 to 64 year old age group, rising sharply to 13% in people over 85 (Mitchell 1995; Smith 2001). The 10-year incidence of early AMD and late AMD was 12.1% and 2.1% respectively in the Beaver Dam Eye Study (Klein 2002). Individuals 75 years of age or older at baseline had significant higher 10-year incidences of both early and advanced AMD (Klein 2002). The main risk factors for the development and progression of AMD include increasing age, smoking and ethnicity. Other reported risk factors include low levels of antioxidants, dietary fat, heart disease, hypertension, genetic influences, alcohol consumption and sun-light (AAO 2006). It should be noted that most of the epidemiologic studies have had few incident cases of advanced AMD on which they have based their conclusions. Also, the length of the interval between population surveys has meant that some incident cases were likely to be missed due to death and that progression of AMD could not be assessed in some cases for the same reason.

Clinical presentation and diagnosis

The early manifestations of AMD are the presence of yellowish deposits known as drusen and/or retinal pigment epithelium abnormalities such as hypopigmentation or hyperpigmentation. In general, these early clinical signs are not associated with significant vision loss. However, a proportion of people with drusen and pigmentary changes will progress to advanced AMD with geographic atrophy (large area of atrophy centered in the macular) and/or development of choroidal neovascularization, both of which can have severe effects on central visual function (AAO 2006; AREDS 2001; CAPT 2004; Smeeth 2005).

Treatment options

Currently the approved treatments for stabilization of vision includes ranibizumab (Lucentis) and pegaptanib (Macugen). Administration of these drugs, however, requires repeat intravitreal injection, and visual recovery is neither complete nor universal. The risks and benefits of long term use also are not known (Vedula 2008). Photocoagulation and photodynamic therapy were shown to have some benefit in preventing severe visual loss but only in a small proportion of patients with the neovascular form of the disease and only for a limited time after treatment (MPS 1991; MPS 1994; Virgili 2007; Wormald 2007). The evidence as to the benefits and harms of surgical injection or implantation of steroids with antiangiogenic properties for treating neovascular AMD is weak (Geltzer 2007). Antioxidant vitamin and mineral supplements were revealed in the Age-Related Eye Disease Study (AREDS 2001) to reduce progression to advanced AMD in persons with intermediate AMD. However, aside from the AREDS formulation, there has been no proven medical intervention for preventing the onset and progression of this disease (Evans 2006; Evans 2008).

Possible mechanisms of statins

The burden of disease would be greatly diminished if a treatment could prevent or delay the onset of early AMD or the progression of early AMD to advanced AMD. Recently, epidemiologic, genetic and pathological evidence has shown a number of risk factors shared by AMD and atherosclerosis, leading to suggestions that statins, which are known to be beneficial in patients with atherosclerotic disease and hyperlipidemia, may also exert protective effects in AMD.

Possible pharmacological mechanisms of statins in preventing AMD include (Guymer 2005a):

- Serum lipid lowering effects: Statins may alter the deposition and/or resorption characteristics of lipids in Bruch's membrane (a thin semi-permeable cellular structure that acts as the basement membrane for the retinal pigment epithelium and effectively mediates metabolic exchange between the retina and the choroid).
- Preserving vascular supply: Statins may preserve vascular supply to the outer retina through a protective effect against atherosclerosis (Friedman 2004).
- The anti-inflammatory actions of statins: Inflammation may be important in AMD pathogenesis (Penfold 2001). The anti-inflammatory properties of statins may provide additional protective effects. Statins down regulate the activation of transcription factors NF-B, AP-1, and hypoxia-inducible factor-1. They therefore have potentially relevant antiinflammatory and antiproliferative effects that are relevant in the treatment of atherosclerotic diseases (Dichtl 2003). Elevated intraocular levels of vascular endothelial growth factor (VEGF) have an important role in the development of choroidal neovascularization (CNV) in AMD. Prior work indicates that statins reduce plasma levels of VEGF and down regulate transcription factors involved in VEGF expression. It is therefore conceivable that systemic statin use may reduce the incidence and progression of CNV via such cellular and molecular effects (Dichtl 2003).
- The antioxidant effect of statins: Oxidized lipids and low density lipoproteins (LDL) may be the initial stimulus leading to inflammation in AMD (Gurne 1991; Spaide 1999). Statins may protect the outer retina, Bruch's membrane and choroid from oxidative damage.
- Inhibition of metalloproteinases: Statins also may inhibit secretion of matrix metalloproteinases, which may be involved in fissuring and rupture of plaques and development of neovascularization (Guymer 2005a).

Rationale for a systematic review

The high prevalence of AMD, the anticipated increase in the aged population and the limited role of available effective treatments highlight the need to search for new treatment strategies that aim at delaying onset or progression of AMD. A number of observational studies have examined the relationship between AMD and the use of statins, and the results have been contradictory. In the Rotterdam Study, those using statins for more than 12 months had a similar incidence of AMD to those not using these drugs (adjusted hazard ratio

1.1, 95% confidence interval (CI) 0.7 to 1.9) (van Leeuwen 2003). In the Beaver Dam Eye Study, the five-year incidence of neovascular AMD was not found to be associated with statin use (odds ratio (OR) 0.9, 95% CI 0.46 to 1.78) (Klein 2001). A more recent study by Klein et al. found that a history of statin use was not associated with the five-year incidence of early AMD (OR 1.16, 95% CI 0.71 to 1.91), progression of AMD (OR 1.16, 95% CI 0.75 to 1.78) or incidence of late AMD (OR 1.27, 95% CI 0.60 to 2.69) (Klein 2007b). Similar negative results were revealed in The Women's Health Initiative Sight Examination (WHISE), an ancillary study to the Women's Health Initiative's clinical trial of hormone replacement therapy (Klein 2007a). One study suggests increased risk with statin use (McGwin 2006). On the contrary, animal experiments showed that pitavastatin (so-called vascular statin) suppressed formation and development of CNV in rats (Sagara 2007). A strong inverse association between statin use and AMD was reported by Hall et al. in a cross-sectional study with 392 participants (OR 0.14, 95% CI 0.02 to 0.83) (Hall 2001) and by McGwin et al. in a study that involved 550 cases of AMD and 5500 controls (OR 0.3, 95% CI 0.21 to 0.45) (McGwin 2003). Tan et al. found that statin use was protective for indistinct soft drusen (hazard ratio 0.33, 95% CI 0.13 to 0.84), a key late AMD precursor lesion, using data from the Blue Mountains Eye Study (Tan 2007). In a population-based cohort study Smeeth et al. assessed the effect of statins on a range of health outcomes. A sample of 129,288 people who initiated treatment with a statin were compared with a matched sample of 600,241 people who did not initiate treatment. Although the hazard ratio of AMD for non-exposed to exposed was 1.17 (99% CI 1.00, 1.38) they found no evidence to support an effect of treatment (Smeeth 2009). Observational and animal studies have methodological limitations and may be subject to various sources of bias and confounding. A systematic collection and summary of currently available data from clinical trials provide the best evidence regarding this issue.

Objectives

The objective of this review was to examine the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and progression of AMD.

Methods

Criteria for considering studies for this review

Types of studies—We included all relevant randomized controlled trials (RCTs) and quasi-RCTs in this review. Studies that did not use randomization to allocate participants but utilized techniques intended to allocate patients in an unbiased fashion were considered to be quasi-randomized trials (e.g., allocation based on day of the week, year of birth, or hospital admission number of consecutive patients).

Types of participants—We included trials that enrolled participants who were diagnosed as having early stages of AMD with no signs of CNV as determined by their study criteria.

Types of interventions—We included trials comparing statins, which inhibit the enzyme 3-hydroxyl 3-methylglutaryl CoA reductase, with other treatments, no treatment, or placebo. We planned to include trials that compared different types of statins therapy, as well as trials

in which statins in combination with another treatment was compared with the other treatment alone.

Types of outcome measures

Primary outcomes: The primary outcome for this review was the change in visual acuity, categorized by 3 or more lines loss, no change (within 3 lines from baseline), 3 or more lines improvement. When continuous LogMAR data were available we analyzed the visual acuity and degree of change as continuous data. The primary timing of outcome assessment was at three years follow-up, with different follow-up times analyzed as reported.

Secondary outcomes: The secondary outcomes for this review were onset and progression of AMD, and were measured as:

1. Incidence of early signs of AMD using definitions specified in the included studies;
2. Incidence of progression from early AMD to intermediate or late stages of AMD using definitions specified in the included studies.

Adverse outcomes: We tabulated all systemic and ocular adverse effects related to either statins or other treatments as reported in the included studies. Specific adverse effects of interest were:

1. Ocular adverse effects;
2. Systemic adverse effects.

Economic data: We planned to document cost-benefit analyses and other data on economic outcomes in the reported studies.

Quality of life data: We planned to assess quality of life data by any validated measures that were presented.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library*, Issue 2, 2009), MEDLINE (January 1950 to April 2009), EMBASE (January 1980 to April 2009), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to April 2009) and the WHO International Clinical Trials Registry Platform (ICTRP). There were no language or date restrictions in the search for trials. CENTRAL, MEDLINE, EMBASE and LILACS were last searched on 30 April 2009 and the WHO International Clinical Trials Registry Platform (ICTRP) was searched on 11 May 2009. See Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4) and ICTRP (Appendix 5).

Searching other resources—We searched the reference lists of the trials included in the review for additional trials. We used the Science Citation Index to find studies that cited the identified trials.

Data collection and analysis

Selection of studies—Two authors independently evaluated the titles and abstracts resulting from the electronic and manual searches to identify potentially relevant studies for inclusion. We obtained full copies of all potentially or definitely relevant articles. Two authors worked independently to determine which studies met the selection criteria. We resolved discrepancies by discussion. We documented the excluded studies and reasons for exclusion in the ‘Characteristics of excluded studies’ table.

Data extraction and management—One Italian speaking colleague (Dr. Gianni Virgili) extracted data from the completed study (Martini 1991). Study characteristics extracted include: study design, participants characteristics, interventions, and the outcomes. This information was verified by a second Italian speaking colleague (Dr. Fabrizio Giansanti). One review author(TL) entered all data into Review Manager (RevMan 5.0).

Assessment of risk of bias in included studies—Two Italian speaking colleagues (GV and FG) assessed the risk of bias of the completed trial according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). The following parameters were considered: 1) sequence generation; 2) allocation concealment; 3) masking (blinding) of participants, personnel and outcome assessors; 4) incomplete outcome data; 5) selective outcome reporting; 6) other sources of bias. Each of the parameters were graded as: ‘Yes’ to indicate low risk of bias, ‘No’ to indicate high risk of bias, and ‘Unclear’ to indicate inadequate information to judge risk of bias.

Measures of treatment effect—We followed guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2008). Martini 1991 reported by arm the decimal visual acuity and standard deviation. The authors, however, did not report the mean difference between the two treatment arms (P-value was mentioned). The mean difference in visual acuity can be calculated based on available data, however, the confidence interval remains unknown because decimal visual acuity generally does not follow a normal distribution.

Dealing with missing data—We contacted authors for additional information. We will update the review as data become available.

Data synthesis—We did not perform a meta-analysis as only one completed trial was identified. We will update the meta-analysis when more data become available.

Sensitivity analysis—We did not perform sensitivity analyses to determine the impact of exclusion of studies with lower methodological quality, exclusion of unpublished studies and exclusion of industry-funded studies at this point because only one completed trial was identified. We will perform a sensitivity analysis when sufficient data become available from additional clinical trials.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search—The electronic searches retrieved 97 titles and abstracts of which five appeared to be relevant and underwent review of the full text. After examining the full text, we excluded three articles and the remaining two articles reporting two distinct trials were included in this review (Guymer 2005; Martini 1991).

Included studies—Martini 1991 was conducted in Italy. A total of 30 participants were enrolled and randomized to receive simvastatin (20 mg/day) or a placebo for three months (see ‘Characteristics of included studies’ table). All patients were 60 years or older and had drusen (no CNV). The patients had good visual acuity and serum cholesterol level > 260 mg at baseline.

Guymer 2005 is an ongoing trial based in Australia. The trial aims to examine the role of cholesterol-lowering medications (‘statins’) in the progression of AMD (see ‘Characteristics of ongoing studies’ table). Participants at high risk of AMD were randomized to receive either 40 mg of simvastatin or placebo for three years. The preliminary results of Guymer 2005 were presented at the 2005 Association for Research in Vision and Ophthalmology (ARVO) annual meeting. By the time of the report, 85 participants had been enrolled, with 60 having completed six months, 42 completed 12 months, and 15 completed 18 months follow-up.

Excluded studies—We excluded three studies; Della Valle 2000a and Della Valle 2000b were not controlled trials and Sen 2002 was a study in patients with diabetic retinopathy (see ‘Characteristics of excluded studies’ table).

Risk of bias in included studies

We graded Martini 1991 as ‘unclear’ for risk of bias (see ‘Risk of bias in included studies’ table) because insufficient methodological details were reported.

Effects of interventions

Within the completed trial (Martini 1991), analyses of 30 participants after three months of treatment showed no statistically significant difference between the simvastatin and the placebo arm in visual acuity (decimal visual acuity 0.21 ± 0.56 in simvastatin arm; 0.19 ± 0.40 in placebo arm). The authors did not report the mean difference and its confidence interval. Visual acuity results also were similar at 45 days after the completion of treatment period (decimal visual acuity 0.20 ± 0.50 in the simvastatin arm; 0.19 ± 0.48 in the placebo arm). The lens and retina status were unchanged during and after the treatment period for both groups. In the ongoing trial (Guymer 2005), analyses of 42 participants (19 in simvastatin arm and 23 in placebo arm) who completed 12 months follow-up showed no statistically significant difference between the two groups in visual acuity, drusen score or

visual function (effect estimates and confidence intervals were not available). We contacted the investigators and will update the review as data become available.

Discussion

This review did not find sufficient evidence to determine the effectiveness and safety of statins for the prevention or delaying the progression of AMD.

This review included one completed and one ongoing randomized placebo-controlled trial. The completed trial (Martini 1991) had a small sample size of 30 participants who were at an early stage of disease. The outcome was assessed at the completion of treatment (three months from baseline) and 45 days afterwards. Because of the slow progressive nature of the disease, the short duration of treatment and follow-up did not provide useful information about the effectiveness of treatment. It may be that it was too short a period of treatment or follow-up to show an effect. In addition, the trial was graded as unclear for risk of bias because of insufficient methodological details. Although no ophthalmological adverse effects were reported during the study period, there was still a degree of uncertainty about the accuracy of this finding because of the short period of follow-up.

We are waiting for the results of the ongoing trial (Guymer 2005). This study includes participants with AMD from both sexes and different ages. The long-term treatment and follow-up of the participants will provide more accurate and reliable information about the effectiveness of treatment and the potential harms.

Authors' Conclusions

Implications for practice

There is insufficient evidence from RCTs to suggest that taking statins may delay the onset and progression of AMD.

Implications for research

The unanswered questions in the prevention and treatment of AMD have led to research opportunities. Because of the slow progressive nature of the disease, a short duration of treatment or follow-up provides limited information about the effectiveness of treatment. In addition, we do not know the stage of AMD at which statins may be effective, nor the potential interactions with other treatment modalities. Further trials are warranted to address these questions and the results of the ongoing trial are awaited. Considering the number of observational studies on this topic, a systematic review of observational studies would provide useful information for planning of new RCTs.

Acknowledgments

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Sources of Support

Internal sources

- Contract N-01-EY-2-1003, National Eye Institute, National Institutes of Health, USA.

External sources

- No sources of support supplied

Characteristics of Studies

Characteristics of included studies *[ordered by study ID]*

Martini 1991

Methods	Randomized, placebo-controlled trial.
Participants	This study included 30 participants with drusen (no CNV), good visual acuity (mean 0.52 LogMAR) and serum cholesterol level > 260 mg. Fifteen participants were randomized into the treatment group and 15 into the control group.
Interventions	HMG-CoA reductase inhibitor (simvastatin, 20 mg/day) versus placebo for 3 months.
Outcomes	The outcomes evaluated were : 1) serum cholesterol levels; 2) visual acuity; 3) microscopic eye exam; 4) fluorescein angiography; 5) ERG, and 6) VEP. Outcome measures were obtained at baseline, 3 months and 4.5 months.
Notes	Article in Italian.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No description was found in the article.
Allocation concealment?	Unclear	No description was found in the article.
Blinding? All outcomes	Unclear	No description was found in the article.
Incomplete outcome data addressed? All outcomes	Unclear	No description was found in the article.
Free of selective reporting?	Unclear	No description was found in the article.
Free of other bias?	Unclear	No description was found in the article.

CNV: choroidal neovascularization

ERG: electroretinography

VEP: visual evoked potentials

Characteristics of excluded studies *[ordered by study ID]*

Della Valle 2000a	Study participants were not randomized. The control arm included participants who refused to use simvastatin for various reasons.
Della Valle 2000b	Study participants were not randomized. The control arm included participants who refused to use simvastatin for various reasons.
Sen 2002	The study was in patients with diabetic retinopathy.

Characteristics of ongoing studies [ordered by study ID]

Guymier 2005

Trial name or title	Age-Related Maculopathy Statin Study
Methods	Randomized, placebo-controlled trial.
Participants	Aimed to recruit participants at high risk of AMD (at least 5 drusen > 125um in both eyes, or one eye with end-stage AMD and the other with signs of early AMD). Inclusion criteria: 1) males and females aged 50 years and older; 2) able to assess the macula in at least 1 eye; 3) visual acuity 6/18 in study eye; 4) high risk drusen in both eyes: 1 or more large soft drusen, > 10 intermediated drusen, or late AMD in one eye and any drusen or pigment change in study eye; 5) normal cholesterol levels; and 6) not currently on cholesterol-lowering medications.
Interventions	Two tablets of simvastatin, 20 mg each, daily, compared to a placebo with an identical appearance for 3 years.
Outcomes	The primary outcome is progression of high risk early AMD to late AMD, evaluated every 6 months. Secondary outcomes are (1) color sensitivity, (2) flicker sensitivity, (3) bleach recovery, and (4) kinetics of dark adaptation.
Starting date	5/01/2003 (Date of first enrolment)
Contact information	Associate Professor Robyn Guymier (rhg@unimelb.edu.au) Center for Eye Research, Australia University of Melbourne, 32 Gisbourne St, East Melbourne, VIC 3002
Notes	Trial reported in ARVO abstract. Trial registration number: ACTRN12605000320651 (registered at WHO International Clinical Trials Registry Platform).

AMD: age-related macular degeneration

Data and Analyses

This review has no analyses.

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Macular Degeneration
- #2 MeSH descriptor Retinal Degeneration
- #3 MeSH descriptor Retinal Neovascularization
- #4 MeSH descriptor Choroidal Neovascularization
- #5 MeSH descriptor Macula Lutea
- #6 macula* near lutea*
- #7 ((macul* OR retina* OR choroid*:TI) AND (degener* OR neovasc*:TI))
- #8 ((macul* OR retina* OR choroid*:AB) AND (degener* OR neovasc*:AB))
- #9 maculopath*
- #10 AMD or ARMD or CNV
- #11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
- #12 MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors
- #13 MeSH descriptor Simvastatin

#14 MeSH descriptor Pravastatin

#15 statin*

#16 HMG near COA near reductase*

#17 hydroxymethylglutaryl near coenzyme near reductase*

#18 hydroxymethyl near glutaryl near coenzyme near reductase*

#19 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#20 (#11 AND #19)

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial. pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp macular degeneration/
14. exp retinal degeneration/
15. exp retinal neovascularization/
16. exp choroidal neovascularization/
17. exp macula lutea/
18. maculopath\$.tw.
19. ((macul\$ or retina\$ or choroid\$) adj3 degener\$).tw.
20. ((macul\$ or retina\$ or choroid\$) adj3 neovasc\$).tw.
21. (macula\$ adj2 lutea).tw.
22. (AMD or ARMD or CNV).tw.
23. or/13-22

24. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
25. exp simvastatin/
26. exp paravastatin/
27. statin\$.tw.
28. (HMG adj3 COA adj3 reductase\$).tw.
29. (hydroxymethylglutaryl adj3 coenzyme adj3 reductase\$).tw.
30. (hydroxymethyl adj3 glutaryl adj3 coenzyme adj3 reductase\$).tw.
31. or/24-30
32. 23 and 31
33. 12 and 32

The search filter for trials at the beginning of the MEDLINE strategy was from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/

19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula degeneration/
34. exp retina degeneration/
35. exp retina neovascularization/
36. exp subretinal neovascularization/
37. maculopath\$.tw.
38. ((macul\$ or retina\$ or choroid\$) adj3 degener\$).tw.
39. ((macul\$ or retina\$ or choroid\$) adj3 neovasc\$).tw.
40. exp retina macula lutea/
41. (macula\$adj2 lutea\$).tw.
42. (AMD or ARMD or CNV).tw.
43. or/33-42
44. exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
45. exp simvastatin/
46. statin\$.tw.
47. (HMG adj3 COAadj3 reductase\$).tw.
48. (hydroxymethylglutaryl adj3 coenzyme adj3 reductase\$).tw.
49. (hydroxymethyl adj3 glutaryl adj3 coenzyme adj3 reductase\$).tw.
50. or/44-49

51. 43 and 50

52. 32 and 51

Appendix 4. LILACS search strategy

macula\$ and degenerat\$ and statin\$

Appendix 5. WHO International Clinical Trials Registry Platform (ICTRP) search strategy

1. “macular degeneration AND statins”
2. “maculopathy AND statins”
3. “AMD AND statins”
4. “macular degeneration AND HMG-CoA reductase inhibitor”
5. “macular degeneration AND lipid lowering”
6. “macular degeneration AND atorvastatin”
7. “macular degeneration AND simvastatin”
8. “macular degeneration AND pravastatin”

References to studies included in this review

- *. Martini E, Scorolli L, Burgagni MS, Fessehaie S. Valutazione degli effetti retinici della somministrazione di simvastatina in pazienti affetti da degenerazione maculare senile. *Annali Di Ottalmologia e Clinica Oculistica*. 1991; 117(11):1121–6.

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Plain Language Summary

Statins for delaying the onset and progression of age-related macular degeneration

Age-related macular degeneration (AMD) is a progressive late onset disorder of the macula affecting central vision. Studies have shown that some of the factors that may lead to atherosclerosis and strokes are the same as those which may lead to AMD. Statins have proved very effective in preventing strokes, so it is possible that they are also protective for AMD. A number of observational studies have examined the relationship between AMD and the use of statins; however, the results have been contradictory.

This systematic review identified one completed and one ongoing randomized controlled trial. Of the completed trial, in which 30 patients received either 20 mg simvastatin or a placebo daily for a period of three months, the analyses did not show a statistically significant difference in visual acuity at completion of study treatment or 45 days after the completion of study treatment. Of the ongoing trial, the preliminary analyses after 12 months of treatment did not show a statistically significant difference between 40 mg simvastatin daily and placebo in visual acuity, drusen score or visual function. Due to the small size of the completed trial and the short duration of the treatment and follow-up period, no conclusion regarding the effects of statins on the onset or progression of AMD can be made at this time. We will update this review as data from the ongoing trial become available.