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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.

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 methods—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2011, Issue 9), MEDLINE (January 1950 to September 2011), EMBASE (January 1980 to September 2011), Latin American and Caribbean

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Health Sciences Literature Database (LILACS) (January 1982 to September 2011), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 16 September 2011.

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.

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 2008; 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 2008). 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 revascularization, both of which can have severe effects on central visual function (AAO 2008; 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 intravitreous 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 2005):

- 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 2005).

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 CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2011, Issue 9), MEDLINE (January 1950 to September 2011), EMBASE (January 1980 to September 2011), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to September 2011), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com),

ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 16 September 2011.

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 included: 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 (Review Manager 2011).

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 2011). 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 to have low risk of bias, high risk of bias, or unclear risk of bias.

Measures of treatment effect—We followed guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). 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

Results of the search—The electronic searches from 30 April 2009 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 included one study (Martini 1991). A report from a conference proceeding of an ongoing study by Guymer published in 2005 is eligible for inclusion in the review and we will include data for this study as it becomes available.

Updated electronic searches on 16 September 2011 retrieved 35 additional titles and abstracts. Of these 35 records, we assessed three in full and excluded two studies (Drobek-Slowik 2008;Maguire 2009) as they were not randomized controlled trials. We included one study by Guymer 2008 which is a further report of the ongoing study first published in 2005. Overall, we reviewed 132 records of which eight underwent review of the full text. Of the eight records assessed at full text, five reporting four distinct studies were excluded and three reporting two distinct trials were included in this review.

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 2008 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 2008 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. In all, 114 participants were enrolled and randomized. Final follow-up and analyses for all participants were expected to be completed in 2010.

Excluded studies—We excluded four studies; Della Valle 2000 and Drobek-Slowik 2008 were not controlled trials, Maguire 2009 was a retrospective study based on a cohort of trial participants, 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 2008), 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 2008). This study included 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.

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.

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External sources

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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. 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 COA adj3 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

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 studies

Martini E, Scorolli L, Burgagni MS, Fessehaie S. Evaluation of the retinal effects of simvastatin in patients with age-related macular degeneration [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.

Excluded studies

Della Valle V, Scorolli L, Meduri R. Retinal effects of Simvastatin in SMD: Cases up-date [Effetti retinici della Simvastatina nella DMS: Aggiornamento casistica]. Annali Di Ottalmologia e Clinica Oculistica. 2000; 126(11-12):249–55.

Della Valle V, Scorolli L, Meduri R. Retinal effects of Simvastatin in patients affected by age related macular degeneration [Effetti retinici della Simvastatina in pazienti affetfi da degenerazione maculare senile correlata all'eta]. Annali Di Ottalmologia e Clinica Oculistica. 2000; 126(5-6):89–95.

Drobek-Slowik M, Karczewicz D, Safranow K, Jakubowska K, Chlubek D. Use of statins as a form of protection against age-related macular degeneration (AMD) [Leczenie statynami jako forma ochrony przed zwyrodnieniem plamki zwiazanym z wiekiem (AMD)]. Klinika Oczna. 2008:1–3. 50–4.

Maguire MG, Ying GS, McCannel CA, Liu C, Dai Y. Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. Statin use and the incidence of advanced age-related macular degeneration in the Complications of Age-related Macular Degeneration Prevention Trial. Ophthalmology. 2009; 116(12):2381–5. [PubMed: 19850347]

Sen K, Misra A, Kumar A, Pandey RM. Simvastatin retards progression of retinopathy in diabetic patients with hypercholesterolemia. Diabetes Research & Clinical Practice. 2002; 56(1):1–11. [PubMed: 11879715]

Studies awaiting classification

Ongoing studies

*. Guymer RH, Dimitrov PN, Varsamidis M, Lim LL, Baird PN, Vingrys AJ, et al. Can HMG Co-A reductase inhibitors (“statins”) slow the progression of age-related macular degeneration? The age-related maculopathy statin study (ARMSS). Clinical Interventions in Aging. 2008; 3(3):581–93. [PubMed: 18982929]

Guymer RH, Robman L, Varsamidis M, Dimitrov P, Hunt N, Lim L, et al. Can HMG Co-A reductase inhibitors (“statins”) slow the progression of AMD? Investigative Ophthalmology & Visual Sciences. 2005; 46 ARVO E-abstract 2364.

Additional references

American Academy of Ophthalmology. [accessed 13 December 2011] Preferred Practice Pattern Guidelines Age-Related Macular Degeneration. www.aao.org/ppp

Age-Related Eye Disease Study Research Group. 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. Archives of Ophthalmology. 2001; 119(10): 1417–36. [PubMed: 11594942]

Complications of Age-Related Macular Degeneration Prevention Trial Study Group. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT): rationale, design and methodology. Clinical Trials. 2004; 1(1):91–107. [PubMed: 16281465]

Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA. 2003; 290(15):2057–60. [PubMed: 14559961]

Deeks, JJ.; Higgins, JPT.; Altman, DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org

Dichtl W, Dulak J, Frick M, Alber HF, Schwarzacher SP, Ares MPS, et al. HMG-CoA reductase inhibitors regulate inflammatory transcription factors in human endothelial and vascular smooth muscle cells. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003; 23(1):58–63.

Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews. 2006; (2) Art. No.: CD000254. 10.1002/14651858.CD000254.pub2

Evans JR, Henshaw KS. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database of Systematic Reviews. 2008; (1) Art. No.: CD000253. 10.1002/14651858.CD000253.pub2

Friedman E. Update of the vascular model of AMD. British Journal of Ophthalmology. 2004; 88(2): 161–3. [PubMed: 14736760]

Geltzer A, Turalba A, Vedula SS. Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews. 2007; (4) Art. No.: CD005022. 10.1002/14651858.CD005022.pub2

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. Journal of the Medical Library Association. 2006; 94(2):130–6. [PubMed: 16636704]

Gurne DH, Tso MO, Edward DP, Ripp H. Antiretinal antibodies in serum of patients with age-related macular degeneration. Ophthalmology. 1991; 98(5):602–7. [PubMed: 1905796]

Guymer RH, Chiu AW, Lim L, Baird PN. HMG CoA reductase inhibitors (statins): do they have a role in age-related macular degeneration? Survey of Ophthalmology. 2005; 50(2):194–206. [PubMed: 15749309]

Hall NF, Gale CR, Syddall H, Phillips DI, Martyn CN. Risk of macular degeneration in users of statins: cross sectional study. BMJ. 2001; 323(7309):375–6. [PubMed: 11509429]

Higgins, JPT.; Altman, DG.; Sterne, JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org

Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992; 99(6):933–43. [PubMed: 1630784]

Klein R, Klein BE, Jensen SC, Cruickshanks KJ, Lee KE, Danforth LG, et al. Medication use and the 5-year incidence of early age-related maculopathy: The Beaver Dam Eye Study. Archives of Ophthalmology. 2001; 119(9):1354–9. [PubMed: 11545642]

Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH. Ten-year incidence and progression of age-related maculopathy: The Beaver Dam eye study. Ophthalmology. 2002; 109(10):1767–79. [PubMed: 12359593]

Klein R, Deng Y, Klein BE, Hyman L, Seddon J, Frank RN, et al. Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: Women's Health Initiative Sight Exam ancillary study. Ophthalmology. 2007; 143(3):473–83.

Klein R, Knudtson MD, Klein BE. Statin use and the five-year incidence and progression of age-related macular degeneration. American Journal of Ophthalmology. 2007; 144(1):1–6. [PubMed: 17475196]

McGwin G Jr, Owsley C, Curcio CA, Crain RJ. The association between statin use and age related maculopathy. British Journal of Ophthalmology. 2003; 87(9):1121–5. [PubMed: 12928279]

McGwin G, Modjarrad K, Hall TA, Xie A, Owsley C. 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors and the presence of age-related macular degeneration in the Cardiovascular Health Study. Archives of Ophthalmology. 2006; 124(1):33–7. [PubMed: 16401782]

Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. Ophthalmology. 1995; 102(10):1450–60. [PubMed: 9097791]

Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. Archives of Ophthalmology. 1991; 109(8):1109–14. [PubMed: 1714270]

Laser photocoagulation for juxtafoveal choroidal neovascularization. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. Archives of Ophthalmology. 1994; 112(4):500–9. [PubMed: 7512336]

Penfold PL, Madigan MC, Gillies MC, Provis JM. Immunological and aetiological aspects of macular degeneration. Progress in Retinal & Eye Research. 2001; 20(3):385–414. [PubMed: 11286898]

Review Manager (RevMan). [Computer program] Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

Sagara N, Kawaji T, Takano A, Inomata Y, Inatani M, Fukushima M, et al. Effect of pitavastatin on experimental choroidal neovascularization in rats. Experimental Eye Research. 2007; 84(6):1074–80. [PubMed: 17418120]

Smeeth L, Cook C, Chakravarthy U, Hubbard R, Fletcher AE. A case control study of age related macular degeneration and use of statins. British Journal of Ophthalmology. 2005; 89(9):1171–5. [PubMed: 16113375]

Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. British Journal of Clinical Pharmacology. 2009; 67(1):99–109. [PubMed: 19006546]

Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, et al. Risk factors for age-related macular degeneration, Pooled findings from three continents. Ophthalmology. 2001; 108(4):697–704. [PubMed: 11297486]

Spaide RF, Ho-Spaide WC, Browne RW, Armstrong D. Characterization of peroxidized lipids in Bruch's membrane. Retina. 1999; 19(2):141–7. [PubMed: 10213241]

Tan JS, Mitchell P, Rochtchina E, Wang JJ. Statins and the long-term risk of incident age-related macular degeneration: The Blue Mountains Eye Study. American Journal of Ophthalmology. 2007; 143(4):685–7. [PubMed: 17386278]

van Leeuwen R, Vingerling JR, Hofman A, de Jong PT, Stricker BH. Cholesterol lowering drugs and risk of age related maculopathy: prospective cohort study with cumulative exposure measurement. BMJ. 2003; 326(7383):255–6. [PubMed: 12560276]

Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews. 2008; (2) Art. No.: CD005139. 10.1002/14651858.CD005139.pub2

Virgili G, Bini A. Laser photocoagulation for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews. 2007; (3) Art. No.: CD004763. 10.1002/14651858.CD004763.pub2

Wormald R, Evans J, Smeeth L, Henshaw K. Photodynamic therapy for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews. 2007; (3) Art. No.: CD002030. 10.1002/14651858.CD002030.pub3

Gehlbach P, Li T, Hatef E. Statins for age-related macular degeneration. Cochrane Database of Systematic Reviews. 2009; (3) Art. No.: CD006927. 10.1002/14651858.CD006927.pub2

Characteristics of studies, Characteristics of included studies

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 table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description was found in the article
Allocation concealment (selection bias)	Unclear risk	No description was found in the article
Blinding (performance bias and detection bias)	Unclear risk	No description was found in the article
Incomplete outcome data (attrition bias)	Unclear risk	No description was found in the article
Selective reporting (reporting bias)	Unclear risk	No description was found in the article
Other bias	Unclear risk	No description was found in the article

CNV: choroidal neovascularization

ERG: electroretinography

VEP: visual evoked potentials

Characteristics of excluded studies

Della Valle 2000	
Reason for exclusion	Study participants were not randomized; control arm included participants who refused to use simvastatin for various reasons
Drobek-Slowik 2008	
Reason for exclusion	Study participants were not randomized; history of statin use for people with AMD compared with people without AMD
Maguire 2009	
Reason for exclusion	Study participants were not randomized to statin use; retrospective study based on a cohort of trial participants
Sen 2002	
Reason for exclusion	The study was in patients with diabetic retinopathy

AMD: age-related macular degeneration

Characteristics of ongoing studies

Guymer 2008	
Study name	Age-Related Maculopathy Statin Study (ARMSS)
Methods	Randomized, placebo-controlled trial
Participants	114 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) were enrolled and randomized. Inclusion criteria: 1) males and females aged 50 years and older; 2) able to assess the macula in at least one eye; 3) visual acuity ≥ 20/60 in study eye; 4) high risk drusen in both eyes: one 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 Exclusion criteria: 1) bilateral end stage AMD; 2) medical or ophthalmic conditions which could potentially affect visual function, such as cataract, diabetes, glaucoma; 3) use of medications that may affect visual function, such as plaquenil, chloroquine, major tranquilizers; 4) currently on cholesterol-lowering medication; 5) use of statins is contraindicated; 6) alanine aminotransferase (ALT) 2 times the upper limit of normal; and 7) previous severe adverse or allergic reactions to statins
Interventions	Two tablets of simvastatin (40 mg 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	Recruitment: April 2003 to end of 2006 Expected completion of follow-up for all participants was 2009-2010
Contact information	Associate Professor Robyn Guymer (rhg@unimelb.edu.au) Center for Eye Research, Australia University of Melbourne, 32 Gisbourne St, East Melbourne, VIC 3002
Notes	Trial reported at ARVO (abstract). Trial registration number: ACTRN12605000320651 (registered at WHO International Clinical Trials Registry Platform)

AMD: age-related macular degeneration