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Statins usage and the risk of cataracts A systematic review and meta- analysis

Thurupu Sowmya *, P.Koteswari, Mukesh, Narsingamma, Aliya Batool, Abdul Bari, Uzma Tasneem

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I. INTRODUCTION

Astatinisaclassofdrugsthataremainlyused to lowercholesterol levels in thebody. Statin drugs works by blocking the actionofacertainchemicalfoundintheliverthatmakescholesterol.Weallneed some level of cholesterol in our bodies. Cholesterol is required forourcellstofunctioncorrectly.Statinshaveshownpromiseasantihypertensivedrugsbecause oftheir abilityto lower both diastolicandsystolicbloodpressure.Themechanismbywhichstatinsacttoreducebloodpressureisunknown.

Statin, also called HMG-CoA reductase inhibitor, drug that acts to lowercholesterollevelsbyinhibitingtheenzyme HMG-CoA(3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which is required for cholesterolsynthesis.Examplesofstatinsinclude simvastatin,pravastatin,andlovastatin. Statins are generally quite safe, but side effects may includemusclepainandfatigue.Arareside effect called myopathy,characterizedbymuscledegeneration, hasbeenassociatedwithamutationinageneinvolvedinmediatingliveruptakeofstatins.

Cataracts are the main cause of low vision and blindness worldwide.1Nearly 13 million people in the United States are reported to suffer fromcataracts.2Statinsarewidelyprescribed to treat hyperlipidemia, astheyreducetheriskofcardiovasculardiseaseConcernaboutthecataractogenic effect of statins arose from animal studies in which dogswereadministeredhighdosesof statins, such as simvastatin,fluvastatin,andlovastatin.10,11However,inhumanstudies,investigationsintotheassociationbetweenstatinuseandtheincidenceofcataractsandcataractsurgery have yielded inconsistent. Cataractsare a main cause of low vision; with the growing elderly population, theincidence of cataracts is likely to increase. Investigators have previouslyhypothesized that statin antioxidant effects may slow the natural agingprocessofthelens.Thereismountingevidence that statins arebeneficial to a wide range of people at risk of cardiovascular disease.14Increasing recognition of the beneficial effects of statins, combined withthe expiry of drug patents for some of the earlier statins, mean that theuseofstatinsislikelytoincreasemarkedly,particularly in thedeveloping world,15 where cataract is the leading cause of blindness. Acataractisacloudingoftheeye'slens.Cataractsaretheleadingcauseof blindness among people older than 55. Most older people have somedegree of lens clouding, which is a normal part of aging. Cataracts aregenerally painless. They usually start out as a small, opaque spot andslowlygrowlarger.Theyfoundthatthe developmentof cataract was27%higherinstatinusers.Researcherspointedoutthatthestudyisnot conclusive and by no means shows a cause-and-effect relationship.However,researchersstatedthatstatinusedoesappeartobeassociatedwithincreasedriskfordevelopingacataract.

Typesofstatins:

Statinsareavailableunderavarietyofgenericandbrandnames,including:

- Atorvastatin(Lipitor)
- Fluvastatin(Lescol)
- Lovastatin(Mevacor,Altoprev)
- Pitavastatin(Livalo)
- Pravastatin(Pravachol)
- Rosuvastatin(Crestor)
- Simvastatin(Zocor)

Statinsareamaincauseofpoorvisionandblind

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ness,specificallyfortheelderly,"saidleadinvestigatorDr.IshakMansi,of the VA NorthTexasHealthSysteminDallas."Thisstudycannotidentifythatstatincausecataracts;rather,itidentifiesstatinuse as associated with ahigherriskofbeingdiagnosedwithcataract,"Thosetakingstatinshada27percentincreasedriskofdevelopingcataractscomparedwithnonusers,theresearchersfound.ItisestimatedthatoneinfourAmericans over age 45 currently takes a statin. In November 2013, theAmericanCollegeofCardi•ologyandtheAmericanHeartAssociationjointlyannouncednewtreatmentguidelinesforhighcholesterolthatlikely will double the number of statin users. Such a significant increaseinstatinusemakesitevenmoreimportanttounderstandIt'salsoimportant to remember that even though cataracts may de•velop as theresultofusinglife-sav•ingmedication,theyaretreatable.Infact,theNationalInstitutesofHealthsaysthatprocedurestoremovecataractsare among the most common and safest surgeries performed in the U.S.This surgery removes the old, clouded lens from the eye and replaces itwithanew,artificial oneto restorethe patient'svisionreportedlinkbetweenstatinuseandcataracts. Cholesterol-lowering statins, whicharetakenbymillionsofpeoplearoundtheglobeatriskfromcardiovascularevents,couldincrease the chance of developingcataracts,alargeUScohortstudyhasfound.Thestudy–ledbyresearchers at Wilford Hall Ambulatory Surgery Centre, in San Antonio,Texas, and funded by the US National Institutes of Health – looked at alargecohortof6,972pairs of statin users and non-users, comparingtheriskofcataractsbetweenthetwogroups.Theresults,publishedintheJournaloftheAmericanMedicalAssociation(JAMA), found thataboutathirdofbothstatinusersandnon-usersdevelopedcataractsduring the study period, althoughthe risk was slightly higher for thelattergroup.However,aseparateanalysisbytheteamsuggestedthattheriskofcataracts couldbemuch higherinthosetaking statinsforprimary prevention (i.e., in patients at risk from cardiovascular diseasewho have not yet suffered a related event, such as a heart attack). Thisanalysis compared 6,113 healthy statin users (with no co-morbidities)with27,400nottakingstatins.Afteradjustingforvariousfactors,includingdemographics,medications,andhealthcareuse,itwasconcludedthat34%ofstatintakerswerediagnosed with cataractsversus 10% of those not taking cholesterol-lowering medication. This isnotthefirsttimealinkbetweencataracts and statins has beenindicated,thoughpriorresearchintotherelationshiphasbeeninconsistent.Inaddition,thestudydidnotfactorinwhetherthetypeofstatinordosagehadanyaffectontherisk.Nevertheless,theresearchersstressthat"therisk-benefitratioofstatinuse,specificallyforprimaryprevention,shouldbecarefullyweighed,"andhavecalledforfurtherstudiestobetterdetermine therelationship between theiruseandcataractdevelopment. Thebenefitsofstatinsarefaroutweighedbyanysmallriskforcataractsurgery. "The development of age-related nuclear cataract might beassociatedwithoxidativestress.Asstatinshaveanantioxidativeeffect,theymightdiminishtheincidenceofage-relatednuclearcataract.Kleinand colleagues, therefore, investigated whether statin use reduced theriskofincidentage-relatednuclearcataractinalongitudinal,population-basedstudy.Thismeta-analysisaimedtoexplorethepreventive effects of combined statin and antihypertensive therapy onmajorcardiovascularoutcomesinpatientswithhypertension.PubMed,Embase, and the Cochrane Library databases and reference lists ofpublished studies were systematically searched throughout October 9,2019.Studiesdesignedasrandomizedcontrolledtrialsandinvestigatingtheeffectsofcombinedstatinandantihypertensivetherapy versus antihypertensive therapy alone were included. Dataabstractionandqualityofincludedstudies wereassessedby2independentauthors.Thesummaryresultswerecalculatedusingrelativeriks(RRs)with95%CIsemployingarandom-effectsmodel.Atotal of 8 randomized controlled trials including 38,618 patients werefinallyenrolled.ThesummaryRRsindicatedthatthecombinedtherapysignificantly reduced the risk of major adverse cardiovascular eventscomparedwithantihypertensivetherapy alone(RR0.79;95%CI0.71–0.88;p<0.001).Furthermore,thepatientsinthecombinedtherapygroupalsoexperiencedlessmyoc

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ardialinfarction(RR0.67;95%CI0.53–0.84;p=0.001)andstrokerisks(RR0.82;95%CI0.72–0.94;p=0.005),whilenosignificantdifferencewasobservedbetweencombined therapyandantihypertensivetherapy alone regarding cardiac death(RR0.96;95%CI0.84–1.08; p =0.465)and all-cause mortality (RR0.95;95%CI0.86–1.04; p =0.277).Thesefindingssuggestedthatcombinedstatinandantihypertensive therapy was associated withmore cardiovascular benefits compared with antihypertensive therapyalone. High blood pressure is more frequently observed in individualsagedmorethan25years,affectingmorethan40%ofadultsworldwide.It is the leading cause of death or disability.The American Society ofHypertensioncollaborationgroupin2009definedhypertensionasaprogressivevascularsyndromecausedbyaseriesofcomplexandinterveningcausesevidencedbyanincreaseinbloodpressure.Furthermore,hypertensionisconsideredasthemostimportantriskfactorforendovascularatherosclerosisandinducesgreateratherosclerotic cardiovascular disease (CVD) risks when combined withothercardiovascularriskfactors.However,theresidualriskofcardiovascular outcomes remains high owing to patients having variouscardiovascularriskfactors.Therefore,combinedstatinandantihypertensivetherapy,evenpolypills,shouldbeusedaccordingtorisk-basedapproaches,andthetreatmentwithcombinedstrategiesshould be based on the absolute risk of cardiovascular outcomes, whichcan yield greater cardiovascular benefits compared with the treatmentstrategy based on a single risk factor. Statins are used as common lipid-loweringdrugsgloballyforpreventing CVD. Recently, a synergisticeffectofcombinedstatinandantihypertensivetherapy contributed tothepreventionofCVDprogression.However,evidencesupportingtheuse of statins combined with blood pressure-lowering medications fortreating patients with grade 1 hypertension, irrespective of cholesterollevels,islacking. Patientswithhypertensionpresentin the moderate-risk categoryshouldbetreatedwithstatins.Moreover,lifestyleinterventionshouldbeimplementedtoimprovebloodpressurelevelsbeforeusingantihypertensiveandstatintreatments.However,studiesreportedinconsistentresultsregardingtheeffectofcombinedstatinandantihypertensivetherapy on major cardiovascular outcomes. Thismight be because recruited patients did not "purely" have hypertension,whichalwayscombinedwithothercardiovascularriskfactors.Inaprevious meta-analysis, combined statins. and intense blood pressure-loweringregimenwerecomparedintermsoftheireffectsonmajorcardiovascularoutcomes,butthestudydidnotexploretheeffectof

addingstatinstoantihypertensivetherapyfortreatingpatientswithhypertension compared with antihypertensive therapy alone. Therefore,thissystematicreviewandmeta-analysisbasedontheavailablerandomizedcontrolledtrials(RCTs)wasconductedtoevaluateandcomparetheeffectsofcombinedstatin and antihypertensive therapyandantihypertensivetherapyalonebased on the patients'characteristics.

II. LITERATUREREVIEW

DanCook2018: Statinuse wassignificantlyassociatedwiththedevelopmentof cataractsin2distinctolderpatientpopulations,according to new findings.The study touched on an important issue inthe treatment of the elderly, who are commonly prescribed statins tomanagecardiovasculardisease(CVD),butwhoalsodemandacceptablevisionthroughoutheirgoldenyears.InvestigatorsusedtheBritishColumbia Ministry of Health database to assess 62,501 Canadian menandwomenwhoaveraged73yearsofageandtookstatinsforatleastayearbeforeundergoing cataractsurgeryandmorethan 650,000matchedindividualswithnohistoryofcataracts.Accordingtothestudy, the adjusted rate ratio (RR) of cataract formation in patients onregular statin use was 1.27, with an adjusted RR of 1.36 for new usersand 1.24 for previous users. The adjusted RR for the long-term use ofstatinsrangedfrom1.14forlovastatinto1.42forrosuvastatin.

Prof.HarryStruijker-Boudier2017;FESCStatinshavereachedapromi

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nentplaceinthecontrolofcardiovascularrisk.The originaltrialsinthe1990sthatshowedtheeffectiveness ofstatinsinreducingcardiovascular risk in coronary heart disease have been followed up bylong-termsafetyandefficacytrials.Thesestudiessupportthewideradoption of statins in primary and secondary prevention strategies. TherecentlypublishedHOPE-3trialmakesa strong case for statintreatmentinpatientswithan intermediateriskwhodonot yethavecardiovasculardisease.Sincehypertensioncontributesimportantlytooverall cardiovascular risk, the use of a statin should be considered inhypertensive patients. However, the individual decision to use a statinshouldbebaseduponindividualisedestimatesofriskreductionandadverseeffects.

AbdullahNassief MD 2008; Statins are widely used to reduce the riskof stroke in patients with coronary artery disease (CAD), but less so inpatientswithoutCAD.Wereviewedrecenttrials fornewevidenceforthe reduction in risk of stroke. In patients with CAD, moderate-intensitystatin treatment has been associated with reductions in risk of stroke,with no increase in hemorrhagic stroke. Additionally, in the TNT trial,intensive lipid lowering provided further stroke risk reduction comparedwithmoderatelipidloweringinpatients withstableCAD.Evidenceisnowavailablethatstatintherapy alsoreducesstrokeriskinpatientswithoutCADbutathighcardiovascularrisk,orwithdiabetesmellitus.The SPARCL trial showed that intensive statin therapy started within 6months after a cerebrovascularevent significantly reduced stroke riskandstrokeseverity.

L Robman& H Taylor 2005: Age and heredity are the most importantrisk factors associated with the different types of cataract. While thehereditary component is self-explanatory, increasing age serves as asurrogate for a number of potential external risk factors, the effect ofwhichiscumulative.Identificationoftheriskfactorsthathaveacausaleffectoncataractdevelopmentmayprovidemeansforcataractprevention.Thereareonlyafewriskfactorsthatsatisfythecriteriaforcausal effect: smoking, which results in the increased risk of nuclearcataract, excessive UV-B exposure and diabetes that increase the riskofcorticalcataract,andsteroidaltreatment, diabetesandionisingradiation that lead to the formation of posterior subcapsular opacity.The effect of medications on cataract development requires furtherstudy,sincetheeffectofthediseasesshouldbedistinguishedfromthatoftreatment.'Stop Smoking'and'UV-Bprotection'campaignsaregaining momentum as preventative measures, while the attempts toactivelypreventcataractwithantioxidantshavenotbeensuccessful.

Phelan and Link 2005; Phelan et al. 2004.: In this study, we examinehowincomegradientsincholesterollevelshavechangedwiththeemergenceof"statins"(or HMG-CoAreductaseinhibitors).Thoughcholesterolwasrecognizedasanimportant risk factor forcardiovasculardiseaseasearlyasthe1960s,itwasnotamenabletoeffectivepharmaceuticalmanipulationuntil the introduction of statinsinthelate1980s.Thisinnovationoffered,for the first time, highlypotent drug control of cholesterol. As an expensive new technology thattreatsanasymptomaticcondition,statinsmay havebeendisproportionately adopted by those with greater resources, promotingdisparities in cholesterol that favor the wealthy. We advance prior workonfundamentalcausetheorybyexaminingaspecificriskfactorformortalityratherthanmortalityitself.Asmortalityismost ofteninfluencedbymyriadfactors,thefindingofvariationinmortalitygradients offers limited insight into precise mechanisms. Furthermore,we consider the role of a specific intervention (statins), instead of relyingonthelessspecificclassificationofcauses ofdeathasmoreorlessresponsivetopreventive measures.We also integrate fundamentalcause theory with two related yet distinct theoretical frameworks. First,we consider a well-established literature on the diffusion of innovations.Second,weconsiderGoldmanandLakdawalla's(2005).

GRIFITHIS(2002): Amini-reviewdouble-blindrandomizedcontrolledtrials(RCTs)wasun

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dertakentoassessthelong-termeffectoflipid-lowering treatments (statins versus placebo) in secondary prevention ofmyocardialinfarction(MI).Thepopulationsamplewasadultpatientswithahistoryof MI,documentedcoronaryheartdiseaseorcoronaryarterydisease.TheCochraneLibraryandthedatabaseMedlineweresearchedandthreeRCTsappearedto possess all the stipulatedinclusionandexclusioncriteria.Thetrialsallcomparedstatinsagainsta placebo; one trial was of simvastatin – the Scandinavian SimvastatinSurvivalStudy(1994)–andthe othertwowereofpravastatin– theCholesterol and Recurrent Events Trial (CARE) (Sacks et al, 1996) andLongtermInterventionwithProvastatinIschaemicDisease(LIPID)(Anon,1998).Thetrialsdemonstratedthatstatinshadaclearandconsistenteffectinsignificantlyreducingtheriskof MI.Overallanapproximatedeclineof30%inMIwasproducedfromthethreetrials.

Newman et al.: Performed a rigorous examination of the safety andtolerability of statins as a class, highlighting differencesamong theagentsasappropriate.Utilizingdatafromrandomizedcontrolledtrials,supplemented with observational data, this review covered both thegeneral adult population as well as sub-groups potentially vulnerableto adverse events including the elderly, children, pregnant women andEastAsians.Italsodiscussedtreatmentofpatientswithchronickidneyand liver disease, HIV, and those undergoing organ transplantation.This commentary is meant to clarify and highlight the salient clinicalpractice lessons we feel both primary and specialty providers should beawareof.

Virmanietal.,2000.: Athinfibrousplaqueatheromaischaracterizedby trimming of the fibrous cap that is infiltrated by macrophages and Tcells with few SMCs, and an increase of extracellular lipids and necroticcoreformation.Suchplaquesarevulnerableandatriskofrupture,therebyevokingatherothrombosis,myocardialinfarctionorstroke.Severalfactorshavebeenproposedtoincreasetherisk of plaquerupture,suchasincreasedcollagendegradationbymatrixmetalloproteinasessecretedbymacrophages,ordecreasedcollagenbiosynthesis because of suppression of SMC activity by interferon-γ, acytokineproducedbyTcells.Clarkeetal.,2006). SMCdeathisseenin thevicinityofmacrophage-richregions of human atherosclerotic plaques (Kockx et al., 1996,1998). Factors that are known to kill SMCscan be macrophage derived (nitric oxide (NO), Fas ligand and tumour-necrosis factor-α) or products formed during oxidative modification oflipoproteinsorcholesterol.Indeed,oxysterols,such as 7-ketocholesterol,mayinducenecrosis(Ghellietal., 2002;Seyeet al.,2004),apoptosisortypeIcelldeath(Lizardetal.,1996,1997;Nishioand Watanabe, 1996; Seyeet al., 2004)orautophagy (Martinet etal.,2004)invascularcells. Autophagicor typeII celldeathisa caspase-independentformofprogrammedcelldeath(GozuacikandKimchi,2004;FerraroandCecconi,2007).Processingofmicrotubule-associatedproteinIlightchain3(LC3)fromthecytoplasmicform(LC3-I)toamembrane-associatedform(LC3-II)isessentialfortheformationofautophagicvesiclesandleadstoincreasedelectrophoreticLC3mobilityonSDS-polyacrylamidegels(GozuacikandKimchi,2004;FerraroandCecconi,2007).

Lynch2003;Pappasetal.1993.: Inaseminalarticlepublishedoveradecadeago,LinkandPhelan(1995)arguedthatsocialfactorssuchas SES can operate as persistent and “fundamental causes of disease”because they are associated with a wide variety of resources that canbemarshaledtoimprovehealthinadiverseandchangingenvironment.To date, however, there have only been a few examples of empiricalsupport or tests of thetheory, and they have generally focused onwhetherSESgradientsinmortalityarestrongerforcausesofdeaththatareconsideredmorepreventable,indirectlyassessingtheroleofresourcesinprocuringpotentialinterventions.

Lynch 2003; Pappas et al. 1993: In a seminal article published over adecade ago, Link and Phelan (1995) argued that social factors such asSES can operate aspersistent and “fundamental causes of disease”because they are associated with a wide variety of resources that canbemarshaledtoimprovehealthinadiversean

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dchangingenvironment.To date, however, there have only been a few examples of empiricalsupport or tests of thetheory, and they have generally focused onwhetherSESgradientsinmortalityarestronger forcausesofdeaththatareconsideredmorepreventable,indirectlyassessingtheroleofresourcesinprocuringpotentialinterventions.

Dr.johnB.kostis: Thebottomlineisthatstatins preventcataracts,"saidDr. John B. Kostis during a presentation at the annual congress of theEuropeanSocietyofCardiology."Butthebottomlineis:Don'tbescaredofcataractswhenprescribingstatins."Theconcernaboutstatins'cataractogenicityaroseinthe1980s,whentheFoodanddDrugAdministration approved lovastatin with the precaution that patientsshouldbeexaminedwithaslit-lampbeforeandduringtreatment.

Dr.WILLIAMS: Therewasalsoa1.4%absoluteriskreduction (Plessthan.0001),demonstratingthat71individuals needed to be treatedwithstatinstopreventone case of cataracts, Dr. Kostis said.Meanwhile,patientswhobeganstatintherapyintheir40shada51%lower chance of cataracts (OR, 0.49), compared with those who beganthe treatment in their 70s and probably already had cataracts (OR,1.03,ornoriskreduction),hesaid."Itispossiblethatthetwoprocesses(aging and statins) work in parallel or interactively," Dr. Kostis said ina news release.In addition, there was a 46% reduction in the risk ofcataracts when patients were treated with statins for as long as 14 years(OR,0.54),comparedwitha10%riskreductionamongthosewhoweretreated for only 6 months (OR, 0.90).Gender did not play a role in thefindings.The meta-analysis had several limitations. Each of the studieshad a different design, and the randomized clinical trials didn't havecataracts as an endpoint. Also, the certainty of exposure to statins inobservationalstudiesisimprecise,andthereisthepossibilityofreporting and publication bias, Dr. Kostis noted.The strength of themeta-analysis was in the consistency of the statins' effect when it wasanalyzedfromvariousaspects,hesaid.Inaddition,allpublishedreports on the topic were included in the analysis. Moreover, the effectof statins in preventing cataracts was significantly more pronounced forthe hard endpoint of cataract extractions.A large, randomized clinicaltrial could put the uncertainty to rest, noted Dr. Kim Allan Williams Sr.,chair of cardiology at Wayne State University, Detroit. But the findingsfrom this analysis were reassuring, added Dr. Williams, who was notinvolvedinthemeta-analysis.Dr.Kostishadnodisclosures.Dr.WilliamshasreceivedconsultantfeesfromAstellasHealthcare.

M.MYOSHI: Sphingosine1-phosphate(S1P)isaserum-borne,naturallyoccurringsphingolipidmetaboliteand ispresentinsubmicromolarconcentrations in normal human sera (Yatomi et al., 1997). Recentstudies have revealed that this lipid is capable of modulating a very widevarietyofbiologicalactivitiesinnumerous organsinmammals(reviewedin(Hla,2003)).Specifically,invascularendothelialcells,S1Pmediates important effects such as migration, survival, proliferation,vasorelaxation and angiogenic morphogenesis (Hla, 2003). Many ofthese effects of S1P are mediated by its binding to and activation of G-protein-coupled S1P receptors, which are expressed at the endothelialcellsurface(reviewedinHla,2001). Fiveindependentreceptorsubtypes, S1P1–S1P5 have been identified in mammals, of which S1P1and S1P3 represent major receptors for S1P expressed in endothelialcells(Leeetal.,1999;Morales-Ruizetal.,2001).Effectormoleculesthatmediate S1P receptor activation to physiological responses of vascularendothelial cells include the endothelial isoform of nitric oxide synthase(eNOS), which in turn is modulated by its upstream protein kinasecascades, phosphoinositide 3′-OH kinase (PI3-K)-Akt (Igarashi et al.,2001a,2001b,2003).Interestingly,S1P,whichwasfoundtobeenriched in high-density lipoprotein (HDL) fractions of normal humansera,mayplaykeyrolesinmediatingHDL-inducedvascularendothelialresponses(reviewedinOkajima,2002).Thus,alterationsinexpressionof S1P1 receptors could potentially influence the responses of

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vascularendothelialcellstoserumlipoproteinconstituents.anvascularendothelial cells, expression levels of S1P1 receptors are subject todynamic regulation by extracellular stimuli, including phorbol esters(Hla and Maciag, 1990) as well as vascular endothelial growth factor(VEGF) (Igarashi et al., 2003). It seemed therefore plausible to us thatstatinsmightmodulateS1P1receptorexpressionlevelsandsubsequent sphingolipid signaling of endothelial cells. In the presentstudies, we provide evidence that statins increase expression levels ofS1P1 receptors and augment eNOS responses to S1P as well as to HDLinculturedvascularendothelialcells.

PETERDRhiggins: Randomizedcontrolledtrialsforpreventingcardiovasculardiseaseindicatedthatstatinshadprovocativeandunexpectedbenefitsforreducingcolorectalcancerandmelanoma.Thesefindingshaveledtotheintensivestudyofstatinsin cancerprevention, including recent, large population-based studies showingstatin-associated reductions in overall, colorectal and prostate cancer.Understandingthecomplexcellulareffects(forexample,onangiogenesisandinflammation)andtheunderlyingmolecularmechanismsofstatins(forexample,3-hydroxy-3-methylglutarylcoenzyme-A (HMG-CoA) reductase-dependent processes that involvegeranylgeranylationofRhoproteins,andHMG-CoA-independentprocesses that involve lymphocyte-function-associated antigen 1) willadvance the development of molecularly targeted agents for preventingcancer. This understanding might also help the development of drugsforotherageing-relateddiseaseswithinterrelatedmolecularpathways.

BA De Waal, MP Buise, AAJ Van Zundert: Statins feature documentedbenefits for primary and secondary prevention of cardiovascular diseaseandarethoughttoimproveperioperative outcomesinpatientsundergoing surgery. To assess the clinical outcomes of perioperativestatintreatmentinstatin-naivepatientsundergoingsurgery,asystematic review was performed. Studies were included if they met thefollowing criteria: randomized controlled trials, patients aged ≥18 yrundergoing surgery, patients not already on long-term statin treatment,reported outcomes including at least one of the following: mortality,myocardial infarction, atrial fibrillation, stroke, and length of hospitalstay.Thefollowingrandomizedclinicaltrialswereexcluded:retrospectivestudies,trialswithoutsurgicalprocedure,trialswithoutan outcome of interest, studies with patients on statin therapy beforeoperation,orpapersnotwritteninEnglish.The literature searchrevealed16randomizedcontrolledstudiesinvolving2275patients.Pooled results showed a significant reduction in (i) mortality [risk ratio(RR) 0.53, 95% confidence interval (CI) 0.30–0.94, P=0.03], (ii) myocardial infarction (RR 0.54, 95% CI 0.38–0.76, P<0.001), (iii) perioperativeatrialfibrillation(RR0.53,95% CI 0.43–0.66, P<0.001),and(iv)lengthofhospitalstay(days,meandifference−0.58,95% CI −0.79 to −0.37, P<0.001) in patients treated with a statin. Subgroupanalysisinpatientsundergoingnon-cardiacsurgeryshowedadecreasein the perioperative incidence of mortality and myocardial infarction.Consequently, anaesthetists should consider prescribing a standard-dose statin before operation to statin-naive patients undergoing cardiacsurgery.However,thereareinsufficient datatosupportfinalrecommendationsonperioperativestatintherapyforpatientsundergoingnon-cardiacsurgery.

MarcusMReidenberg: The painful or tender myopathy with elevatedCPK due to statin drugs is well described and uncommon [1, 2]. StatinmyopathycanalsooccurwithoutelevatedCPKorpain[3,4]Morecommon is a feeling of lack of energy in people taking these drugs. Sincestatinsblockmevalonatesynthesis[5],theylowerlevelsofubiquinone,an essential compound for mitochondrial energy production, as well aslowering cholesterol. Thus, these people may truly lack energy. A fewpeople who described lack of energy or having aged rapidly while onstatins were advised to take ubiquinone (co-enzyme Q10, Co-Q10) whilecontinuingthestatin.Theirenergylevelimprovedandtheyfeltbetter.Arandomizeddouble-

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blindtrialcomparing35mgCo-Q10bidwithplacebobidwasinitiatedafterapprovalbytheWeillCornellIRBforpatientsonstatinswhofeltlackofpeporenergysince starting thestatinsandwhodidnothavemusclepain,tenderness, or elevatedCPK.Bythetimethistrial started, most patients in my geographicalareawiththesesymptomseither stopped the statin or started Co-Q10ontheirown,thusonlythreesubjectswereaccruedin1.5yearsandthe trial was stopped.The subjects' ages were 68, 69, and 75. PlasmaCo-Q10levelsweremeasuredbysamplepretreatment with1,4-benzoquinonetochangethereducedformofCo-Q10tothe oxidizedform,precipitationwith1-propanol,andassayedonanHPLCwithred-oxelectricalchemicaldetectioninthelaboratoryof DrMFBeal[6,7].

FatimaMraiche,JonathanCena: Althoughstatinshavebeenreportedtoinhibitthepropro- endothelin- 1(ET- 1)genetranscriptioninendothelial cells,theireffectsonthevascularfunctionofET- 1 havenotbeenexplored.We,therefore,examinedtheeffectsofstatinsoncontractionandDNAsynthesismediatedbyET- 1invascularsmoothmuscle. TheeffectsofstatinsoncontractioninducedbyET- 1werecomparedtothosemediatedbynoradrenaline(NA)andKCl.2Simvastatin (SV) induced a concentration- dependent relaxation of toniccontractionmediatedbyET- 1(10nm)(IC50valueof1.3µm).Therelaxationwasalsoobservedinringsprecontractedwith NA(0.1µm)andKCl(60mm).Incontrast,pravastatin did not have any effect onthecontractions.3Endothelialdenudationor pretreatment with l- NAMEdidnotpreventtherelaxation,but did reduce the relaxantactivityofSV.4SVpreventedRhoactivationcausedbyET- 1andKClin aortic homogenates, as assessed by a Rho pulldown assay. 5 The RhokinaseinhibitorHA- 1077mimickedtheeffectsofSVon toniccontractionsinducedbyET- 1,NAandKCl.

MehboubAhmed: Amini-review(Griffiths,2002)ofdouble-blindrandomized controlled trials (RCTs) was undertaken to assess the long-termeffectoflipid-loweringtreatments(statinsversusplacebo)insecondarypreventionofmyocardialinfarction(MI). Thepopulationsample was adult patients with a history of MI, documented coronaryheart disease or coronary artery disease. The Cochrane Library and thedatabaseMedlineweresearched and three RCTs appeared to possessallthestipulatedinclusionandexclusion criteria. The trials allcompared statins against a placebo; one trial was of simvastatin – theScandinavianSimvastatinSurvivalStudy(1994)–andthe other twowere of pravastatin – the Cholesterol and Recurrent Events Trial (CARE)(Sacksetal,1996)andLongtermIntervention with ProvastatinIschaemic Disease (LIPID) (Anon, 1998).The trials demonstrated thatstatinshadaclearandconsistent effect in significantly reducing therisk of MI. Overall an approximate decline of 30% in MI was producedfromthethreetrials.

HALBERTL.WHITE: Weperformedarandomized,double-blind,placebo-controlledtrialwithequalallocationtosimvastatin,20mg;pravastatinsodium,40mg;orplacebofor 6months.Ninehundredseventy-threemenandwomen without known cardiovascular diseaseor diabetes mellitus, with low-density lipoprotein cholesterol screeninglevels of 115 to 190mg/dL, had assessment of systolic and diastolic BP(SBP and DBP, respectively). Blood pressure values were compared forplacebovsstatinsbyintention-to-treat(ITT)analysis. Additionalanalyses were performed that (1) were confined to subjects with neitherhighbaselineBP(SBP>140mmHgorDBP>90mmHg)norreceivingBPmedications,toexcludegroupsinwhomBPmedicationsormedication changes may have influenced results, and (2) separatelyevaluated simvastatin and pravastatin (vs placebo). The time course ofBP changes after statin initiation and the effect of stopping statins onBPwereexamined.ReductionsinSBPandDBPoccurredwithhydrophilicandlipophilicstatinsandextendedtonormotensivesubjects. These modest effects may contribute to the reduced risk ofstrokeandcardiovascularevents reportedonstatins.

DharaniYerrakalva,SimonJGriffin: TheNationalInstituteforHealthandCareExcellence(NICE)guidelinesonlipidmodificationadviseo

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ffering statins for primary prevention to patients with over 10% 10-year modelled risk of a cardiovascular event, a change from 20%. Thishas generated controversy among clinicians, researchers, and journaleditors. Patients already taking statins were more likely to stop takingthem after the intense media coverage between March and October2014, though there was no associated change in initiation. 1 Clinicians'worrieswerecrystallisedinaletterof concernfromleadingUKmedicalfigures to NICE concerning the frequency of adverse events and themagnitude of the effectiveness of statins. 2 Two sources of evidencewere cited regarding risk levels, the meta-analyses by the CholesterolCollaborationTrialists(CTT)Coll aborationandCochrane.

KJGash,ACChambers,DECotton, AC Williams,
MGThomas: Completetumourresponse(pCR)t oneo-adjuvantchemo-radiotherapyforrectalcancerisassociatedwithare ductioninlocalrecurrenceandimproveddisease-freeandoverallsurvival,butisachieved in only 20–30% of patients. Drug repurposing for anti-cancertreatmentsisgainingmomentum,butthepo tentialofsuchdrugsasadjuncts, to increase tumour response to chemo-radiotherapy in rectalcancer, is only just beginning to be recognised. A systematic literaturesearch was conducted and all studies investigating the use of drugs toenhanceresponsetoneo-adjuvantradiationinrectalcancerwereincluded. 2137 studies were identified and following review 12 studieswere extracted for full text review, 9 studies were included in the finalanalysis. Aspirin, metformin and statinsare associated with increaseddownstaging of rectal tumours and thus may have a role as adjuncts toneoadjuvanttreatment,highlightingaclearneed forprospectiverandomised controlled trials to determine their true impact on tumourresponseandoverallsurvival.

AlexandrosBriasoulis,VikramAgarwal: Inex perimental studies,statinshavebeenshowntolowerbloodpre ssurethroughincreasednitricoxidebioavailabilit yandimproved arterial compliance. Theclinicalsignificanceofthiseffectremainspoor lydocumented. Theauthorsperformedameta-analysisoftheeffec tofstatinsonsystolicbloodpressure(SBP)anddias tolicbloodpressure(DBP)includingprospectiver andomized,controlledtrials of statin therapy. EMBASEandMEDLINEsearchesforstudiesinw hichpatientswererandomizedtotreatmentwithas tatinplusstandardtreatment(orplacebo)vsstanda rd treatment (or placebo) were conducted. Studies that provideddataonSBPandDBPvaluesbeforetheini tiationofthetreatmentandattheendofthefollow-u pperiodwereincluded.Atotalof40studieswith51 comparisongroupsexamining22,511controlsan d22,602patientstakingstatinswereexamined.Me anSBPinthestatingroupdecreased by 2.62 mm Hg (95% confidence interval [CI], −3.41 to −1.84;P<.001)andDBPby0.94mmHg(95%CI,− 1.31to−0.57;P<.001).In studiesincludinghypertensive patients, the decrease in bloodpressureswithstatinswasslightlygreater(S BP,−3.07mmHg;95%CI, −4.00 to −2.15 and DBP, 1.04; 95% CI, −1.47 to −0.61). Similarly, statins effectively reduced SBP in diabetic patients. In this large meta- analysis of prospective controlled studies, the authors found a smallbut statistically significant reduction of SBP in patients taking statins.Thedecreaseinbloodpressuremaycontr ibutetothepleiotropiceffectofstatinsinreducin gcardiovascularrisk.

XiaoyuZhang, Jianzhong Wen, Zhiqiang Zhang: Previous studieshave indicated that statins use is associated with risk of dementia, butpresented controversial results. Medline,Embase, Web of Science, andtheCochraneDatabaseweresearchedupdatet oNovember2017toidentifythepotentialrelations hipbetweenstatinsuseanddementia.Thirty-oneeligiblestudiesinvolvingatotalof3332, 706 participantswith184,666incident cases were included in this meta-analysis.Statins use was associated with dementia risk decrement (relevant risk[RR]: 0.85; 95% confidence interval [CI], 0.80–0.89). Subgroup analysisshowedstatinsusewasassociatedwithAl zheimer disease (AD)(RR:0.81;95%CI,0.73–0.89)andnon-ADdementia(RR:0.81;95%CI, 0.73–0.89)riskdecrement.Furthermore, statins use was associatedwith dementia risk decrement in female (RR: 0.89; 95% CI, 0.80–0.98)and male (RR: 0.88; 95%CI, 0.83–

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0.93). In addition, a dose–responseshowed per 1 year of duration of statins use incremental increase wasassociated with 20% dementia risk decrement (RR: 0.80; 95% CI, 0.73–0.87),andper5-mgmean daily dose incremental increase in statinsusewasassociatedwith11%dementiariskdecrement(RR:0.89;95%CI,0.83–0.96).Statinsusewas associated with dementia riskdecrement. The potency and the cumulative duration of statin utilizedplayedcriticalroles.

Fauchier et al.:also provided evidence on antiarrhythmic effect ofstatins [8], and a number of randomized trials have been publishedsince then. Thus, we aimed to conduct a meta-analysis to evaluate theeffectofstatinuseontheend-pointofincidenceorrecurrenceofAF.

JADAD et al.[30]. The number of events in each trial was extracted onthebasisoftheintention-to-treatapproach.Alltheanalysesontheend-pointofAFwereperformedatthetriallevel,andnoneofthedataoftheindividualstudieswereobtainedfromsponsoringinstitutions.

Hodicketal,16Schliengeretal,24Smeethetal,25CollinsandAltman,18andTanetal,26weused theweightedaverageofage-adjusted hazard ratios and the number of cataracts in the comparisongroups to calculate the number of cataracts in the active groups. In thestudybyHaveletal,wherenoopacitieswereobservedineithertheplaceboorlovastatingroup,weentered1cataractin each group inorder to avoid division by 0 to obtain an odds ratio (OR).27 The specificstatin,typeofstudy(randomizedvsobservational),durationoffollow-up in months, percentage of patients who were men, and average agewererecorded.Lovastatinwasusedin3 studies,17,22,27 andsimvastatin in 4 studies.19,23,28 In 7 studies, more than 1 statin wasused,andthedatawerepresentedintheaggregateratherthanbyindividual statin. The following statins were used in these 7 studies: inthe study by Tan et al, simvastatin, fluvastatin, lovastatin, atorvastatin,andpravastatinwereused.

Pedersenet al, cataract was not the primary end point, and the datawere derived by the authors in a post hoc analysis.23 In studies whereall pertinent information was not included in the primary publication ofthe trial, we used other publications from the same studyin order toobtainthedata.Whenspecificdataontherateoftheoccurrenceofcataract were not included in the publications, we contacted the seniorauthorstoobtaintherequisiteinformation. Whenthedoseoftheindividual statins used was known, the relative dose was calculated bymultiplying the dose used times the relative potency (1 for lovastatin,fluvastatin,and pravastatin; 2 for simvastatin; 4 for atorvastatin; and8 for rosuvastatin).29–31 Metaregression of studies with known relativepotency was performed. There were no studies using either atorvastatinorrosuvastatinalone.

Dr. Mark Fromer, an ophthalmologist at Lenox Hill Hospital in NewYorkCity,saidcataractsareverycommon. "Inone'slifetime,thechanceofdevelopingacataractis100percent,"hesaid."Thegoaliswewanttokeep you alive long enough to get one, and that's where statins comein," he said. "Statins increase the length of life by decreasing strokesand heart attacks."Cataracts can be treated with surgery that is "quick,painless and 99.9 percent successful," Fromer said. "So, since you aregoing to get a cataract anyway, you might as well take your statin -- it'sinyourbestinterest."

KleinBEKetal.(2006) Statinuseandincidentnuclear cataract.JAMA295:2752–2758Thedevelopmentofage-relatednuclearcataractmightbeassociatedwith oxidativestress.Asstatinshaveanantioxidative effect, they might diminish the incidence of age-relatednuclear cataract. Klein and colleagues, therefore, investigated whetherstatin use reduced the risk of incident age-related nuclear cataract in alongitudinal, population-based study.Of the 2,962 participants in thethirdexaminationoftheBeaverDamEyeStudycohort,1,299hadgradable slit-lamp photographs of both eyes, and were considered atrisk of developing incident nuclear cataract within 5 years. Over the 5-

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year follow-up period, the incidence of nuclear cataract was 12.2% instatin users (17.2% in nonusers). Participants who developed nuclearcataracts were more likely to be older, female, less educated, and had alower income than those who did not. Statin use was associated withnearly half the risk of developing nuclear cataract. After adjusting fortotalcholesterollevel,smoking,anddiabetes ,therelationshipbetweenstatinuseandcataracti ncidencewasnotsignificantlyaltered.

Bang et al1 report that randomized treatment with simvastatin plusezetimibewasassociatedwitha44%loweri ncidenceofcataractsintheSimvastatin and Ezetimibe in Aortic Stenosis Study (SEAS) trial. Meta-analysis including the SEAS trial and previous studies indicates thatthe statin use is associated with a clinically and statistically significantdecrease in the occurrence of cataracts. The findings of SEAS confirmtheresultsofourpreviousmeta-analysis,2whereasignificantprotective effect of statins was observed in 8 observational studies (oddsratio [OR] 0.81, 95% CI 0.70 to 0.93, p = 0.004), whereas an effect ofsimilar magnitude was observed in the 6 randomized trials but did notreach statistical significance (OR 0.84, 95% CI 0.67 to 1.05, p = 0.119).When the SEAS trial was added to our meta-analysis of randomizedtrials, the effect became statistically significant (OR 0.78, 95% CI 0.63to0.95,p=0.0165).Thus,statinsexertaprot ectiveeffectinpreventingcataractsthatisclinica llyandstatisticallysignificantandisprimarilyo bservedinyoungersubjectsandwithlongerdura tionofstatintherapy.

TobertJA,etal. StatinSafetyandAssociatedA dverseEvents:AScientificStatementFromthe AmericanHeartAssociation.ArteriosclerThro mbVascBiol2018.Recently,theAmericanHea rtAssociationreleasedacomprehensivescientif icstatementregardingthesafetyandtolerability ofstatintherapy.Thereviewcomesatanimporta nttimeassocietal guidelines continue to recommend the broader use of statintherapy. Statins remain among the most prescribed medications by USclinicians.Newmanetal.performedarigoro usexaminationofthesafety and tolerabilityof statins asa class, highlighting differencesamongtheagentsasappropriate.Uti lizingdatafromrandomizedcontrolled trials, supplemented with observational data, this reviewcoveredboththegeneraladultpopulatio naswellassub-groupspotentiallyvulnerabletoadverseeventsi ncludingtheelderly,children,pregnantwomen andEastAsians.Italsodiscussedtreatmentofpat ientswithchronickidneyandliverdisease,HIV, andthoseundergoing organ transplantation.This commentary is meant to clarifyand highlight the salient clinical practice lessons we feel both primaryandspecialtyprovidersshouldbeaware of.

Dr.ClydeYancey,cardiologychiefatNorthw esternMedicineinChicago,saidtheresultsaddi mportantevidencefavoringdrugtreatmentforl ower-riskpatients,butemphasizedthatlifestyleappro aches including diet and activity should be included. He wasn'tinvolvedintheresearch.Thestudyused1 0milligramsdailyofrosuvastatin, sold as a generic or under the brand name Crestor. Theauthors of the related editorial said other statins would likely havesimilarresults.Crestor'smaker,AstraZen eca,andtheCanadianInstitutesofHealthResear chpaidforthestudy.Yusufreportedreceivinggr antsfromboth;severalco-researchersreportedgrantsandpersonal fees from the company and other drug makers.The bloodpressuredrugswerecandesartan,soldasa genericandbyAstraZenecaasAtacand;andhyd rochlorothiazide,agenericdiuretic.

Bill Sardi what statins teach is that modern medicine would rathertreat everybody to find the one who might benefit, rather than targetthehigh-riskindividual.Amongadultmalestheriskforas udden-deathheartattackisnotaddressedbystatins.Tho sedrop-deadheartattacksareactuallyelectricalstormsth atneedtobeaddressedbytheprovisionofelectro lytes,namelypotassiumandmagnesium.Since alcoholdrinkershavelowlevelsofthesetwominer als,maybethemineralsshouldbeaddedtothebooz eandthatwould be that. But no,

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theremustbesomethingforthecardiologisttodoto earnaliving.Sowehaveto find another type of heart attack. That would be the clotting heartattack,something.

Dear Dr Jha,I am unable to imagine rosuvastatin (Crestor) as a divinegloryofVishnu.IamabletoenvisionHOP E-3asanevenmoreegregious example of a marketing trial than JUPITER, the trial thatcreatedthemythologythaths-CRPquantificationalonemarksapopulationtha tshouldbetreatedwithCrestordespitenormalch olesterol levels. The JUPITER trial leaves legacies of medicalization,ofincreasedequityforAstra-Zeneca,andofahighbarfordatatorturing. I made these pointswhen JUPITER firstappeared in theNEJM Along comes HOPE-3, the same exercise in data torturing butnow targeting people declared to have "intermediate risk". Some 13,000people were recruited in 228 centers in 21 countries. Statisticians andepidemiologists were hired to tease a tiny reduction in clinical outcomesout of all this heterogeneity in a RCT conducted over the course of 5+years.

CarlosA.Feldstein,MD Thereisconsiderableevi dencethathypertensionanddyslipidemiaareinter -relatedmetabolically,epidemiologically, and clinically[1,2]. The association of hypertension anddyslipidemiaconfersagreaterincreasein cardiovascular risk thanwouldbeexpectedwitheitherriskfactoralone [3].Withregardtothisrelationship,arecentanalysis ofdataoftheNational Health andNutritionExaminationSurvey 2003-2004 showed that the prevalenceof hypertension was ranged from 23.1% in those without cardiovascularcomorbiditiesto51.8%to81.8%in thosewithcardiovascularcomorbidities (in chronic kidney disease: 81.8%; in diabetics: 76.8%; inperipheral artery disease: 73.7%; in coronary artery disease: 73.0%; incongestive heart disease: 71.4%; in stroke:69%; in metabolic syndrome:61.5%; in dyslipidemia: 51.8%). In spite of higher rates of hypertensiontreatment in patients with cardiovascular comorbidities (83.4%-89.3%)thaninthosewithoutheseconditions(66. 5%),controlratesfortreatmentremainedlow(23.2 %-49.3%)[4].Theremarkablebenefitachievedwithst atintreatmentsinpatientswithawiderangeofchol esterol levels cannot be attributed only to their cholesterol loweringeffectalone.

AlexandrosBriasoulisMD,VikramAgarwal MD,MPH,FranzH.Messerli MD In experimental studies, statins have been shown to lowerbloodpressurethroughincreasednitricoxid ebioavailabilityandimprovedarterialcompliance.Theclinicalsignificanceofthiseffectremains poorly documented. The authors performed a meta-analysis ofthe effect of statins on systolic blood pressure (SBP) and diastolic bloodpressure(DBP)includingprospectiverand omized,controlledtrialsofstatintherapy.EMBA SEandMEDLINEsearchesforstudiesinwhichpa tientswererandomizedtotreatmentwithastatinpl usstandardtreatment(orplacebo)vsstandardtreat ment(orplacebo)wereconducted.Studiesthatpro videddataon SBP and DBP values beforetheinitiationofthe treatmentandat theendofthe follow-up periodwereincluded.Atotalof40studieswith51c omparison groupsexamining22,511controlsand22,602pati entstakingstatinswereexamined.

KyriakoulaMerakou,AnastasiaBarbouni The purposeofthis studywas to determine whether patients undergoing cataract surgery whilelistening to meditation music experience lower levels of blood pressureandheartrate.Twohundredindividualsu ndergoingcataractsurgeryparticipatedinthestud y.Hundredindividualslistenedtomeditationmusi c,throughheadphones,beforeandduringtheopera tion(intervention group) and 100 individuals received standard care (controlgroup).Patientsstresscopingskillswere measuredbytheSenseofCoherence Scale (SOC Scale). Systolic and diastolic blood pressure andheartrateweredefinedasoutcomemeasures.

Wen- tongFang,Hong- jianLi,HaiboZhan g,SuJiang Meta- analysisofrandomized,cont rolledtrialswithuseofstatinsonincidenceorrec urrenceofAFwasperformed. Theuseofstatinshasbeensuggestedto protect against atrial fibrillation (AF) in some clinical observationaland experimental studies but has remained inadequately explored. Thisstudy was designed to examine whether statins can reduce the risk ofAF.

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GianluigiSavarese,AntonioMGotto,StefaniaPaolillo In elderlypatientswithpreviousCVevents,theuseofstatinsisrecommendedbyguidelines,whereasthebenefitsofthesedrugsinelderlysubjectswithoutpreviousCVeventsarestilldebated.Randomizedtrialscomparingstatinsversusplaceboandreportingall-causeandCVmortality, myocardial infarction (MI), stroke, and new cancer onset inelderly subjects (age ≥65 years) without established CV disease wereincluded. In elderly subjects at high CV risk without established CVdisease, statins significantly reduce the incidence of MI and stroke, butdonotsignificantlyprolongsurvivalintheshort-term.

ImadM.Tleyjeh,MD,MSc,FayazA.Hakim,MD,Emergingepidemiologicalevidencesuggeststhatstatinusemayreducetheriskof infections and infection-related complications. Our objective was toexaminetheassociationbetweenstatinuse andthe risk of infectionsand related outcomes.We searched several electronic databases frominceptionthroughDecember2007forrandomizedtrialsandcohortstudiesthatexaminedtheassociationbetweenstatinuseandtheriskoroutcomeof infections. Data on study characteristics, measurementofstatinuse,outcomes (adjusted for potential confounders), andqualityassessmentwereextracted.

III. AIM AND OBJECTIVE

Aim:
Todeterminewhetherstatinsusageaffectstheriskofcataracts.

Objectives:

1) Assess the risk of cataracts and cataract surgery among users ofstatins.
2) Perform subgroup analyses based on study design, type of statin,the methodological quality of the study, study location, age, sex,follow-upduration,outcomeandoutcomeassessment.

We conducted this meta-analysis following the guidance providedby the Cochrane Handbook29 andperformed the literature search,articlescreening,studyselection,qualityevaluation,anddataextraction.

SearchCriteria
TheCochraneLibrary,PubMed,andEMBASEdatabaseswere searchedfrom January 2000 to January 2022 for English language publications,includingabstracts. Thesearchwasperformedusingthefollowing terms:"statinsORHMG-CoA reductase inhibitors OR Simvastatin OR Lovastatin OR FluvastatinORPravastatinORRosuvastatin ORAtorvastatin"AND"cataract." We also manually searched for relevant articles from the reference listsoftheretrievedarticles.

InclusionCriteria
Studieswereincludedinthismeta-analysisiftheymeetthebelowcriteria:

(1) Thestudyshouldbecase–control,cohortstudy,orrandomizedcontrolledtrials(RCTs)
(2) Non–statinusersshouldbeincludedinthecomparisongroup
(3) Cataractsand/orcataractsurgeryshouldbeoutcome
(4) The association between statin use and the risk ofcataracts/cataractsurgeryshouldbe investigated

ExclusionCriteria
Studieswereexcludedinthismeta-analysisiftheymeetbelowcriteria:

1) Basicsciencestudies
2) reviews,
3) editorials/letters
4) casereports
5) studieswithoutcomparisongroups

DataExtractionandQualityAssessment
Dataextractionwasperformedandthefollowinginformationwasextracted from each study: the last name of the first author, year ofpublication, study design, country of origin of the population studied,patientcharacteristics,statinuse,informationsourceforexposureascertainment,riskestimatesandcorresponding95%CIs,andcovariatesadjustedforinthemultivariableanalysis.Forstudiesthatprovided more than 1 risk estimate, we extracted the estimate that wasadjusted forthe

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greatestnumberofconfounding factors. We assessedthemethodologicalqualityoftheincludedstudiesbasedontheNewcastle-Ottawa Scale (NOS) for observational studies, 31 which wasdevelopedtoassessthequalityofnonrandomizedstudiesinmeta-analysis.Usingthisscale,observationalstudies werescoredacross3categoriesasfollows:selection(4questions)andcomparability(2questions)ofthestudygroupandascertainmentoftheoutcomeofinterest (3 questions), with all questions having a score of 1 except forthecomparabilityofstudygroups,forwhichseparatepointswereawarded for controlling for age and/or sex (maximum, 2 points). A scoreof ≥7 points was suggestive of a high-quality study. The quality of theincludedRCTswasassessedbyCochraneriskofbiasassessment,29which allots scores for the following: random sequence generation (1),allocation concealment (1), blinding of participants and personnel (1),blindingofoutcomeassessment(1),incompleteoutcomedata(1),selective reporting (1), and other sources of bias (1). Scores of 1 to 4indicatelowquality,andscoresof5to7indicate highquality.

OutcomesAssessed

The primary analysis focused on assessing the risk of cataracts andcataract surgery among users of statins. We also performed subgroupanalyses based on study design (case–control, cohort, or RCT), type ofstatin, the methodological quality of the study (high or low), studylocation (Europe, North America, Asia or Australia), age, sex, follow-upduration, outcome and outcome assessment, and whether potentialconfounders were included in the adjusting model (eg, low-densitylipoproteinincluded/missing,cardiovasculardisease[CVD]included/missing,smokingincluded/missing).

By searching the 3 databases, 497 potentially eligible articles wereidentified.Intotal,336articleswereexcludedafterreadingthetitleandabstract, and the full texts of theremaining 161 articles were evaluatedin detail. Of these 161 articles, 17 met our inclusion criteria.17 studiesconsisting of 6 cohort studies, 6 case–control studies, and 5 RCTs wereincludedinthemeta-analysisandinvolvedmorethan3,13200cataractcases.

Table:1CharacteristicsoftheIncludedStudies

PublishedYear	Author	No.ofsubjects		IncidenceOccurred	Risk%
2006	Barbara E.K.Klein	Nostatinused (Controls)	4078	478	11.72143
		StatinsUsed(Cases)	1041	109	10.4707
2006	Jennifer S.L.Tan	Nostatinused (Controls)	5562	1320	23.73247
		StatinsUsed(Cases)	376	71	18.88298

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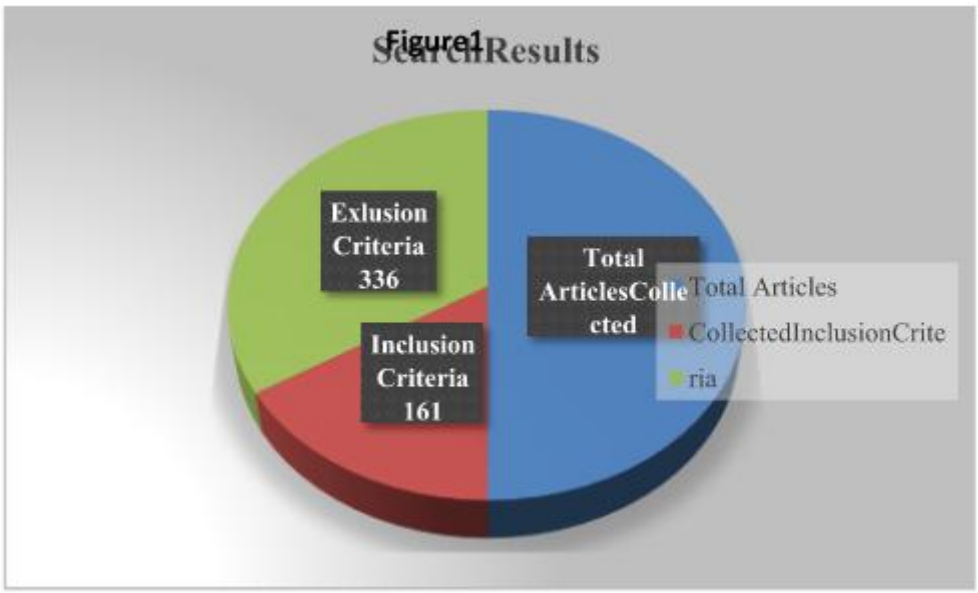

Figure1

Table2:CharacteristicsoftheCohortStudies

PublishedYear	Author	No.ofsubjects		Incidence Occurred(Cataract/CataractSurgery)	Risk%
2006	BarbaraE.K. Klein	NoStatinsUsed (Controls)	4,078	478	11.7
		Statins Used(Cases)	1,041	109	10.5
2006	JenniferS.L.Tan	NoStatinsUsed (Controls)	5,562	1,320	23.7
		Statins Used(Cases)	376	71	18.9
2010	JuliaHippisley-Cox	NoStatinsUsed (Controls)	1,757,933	26,611	1.5
		Statins Used(Cases)	213,085	9,930	4.7
2011	Carol JWaudby	NoStatinsUsed (Controls)	12,496	2,874	23.0
		Statins Used(Cases)	5,402	604	11.2
2013	Chao-LunLai	NoStatinsUsed (Controls)	419,323	16,137	3.8
		Statins Used(Cases)	30,844	1,533	5.0
2013	JessicaLeuschen, MD	NoStatinsUsed (Controls)	32,623	4,504	13.8
		Statins Used(Cases)	13,626	437	3.2

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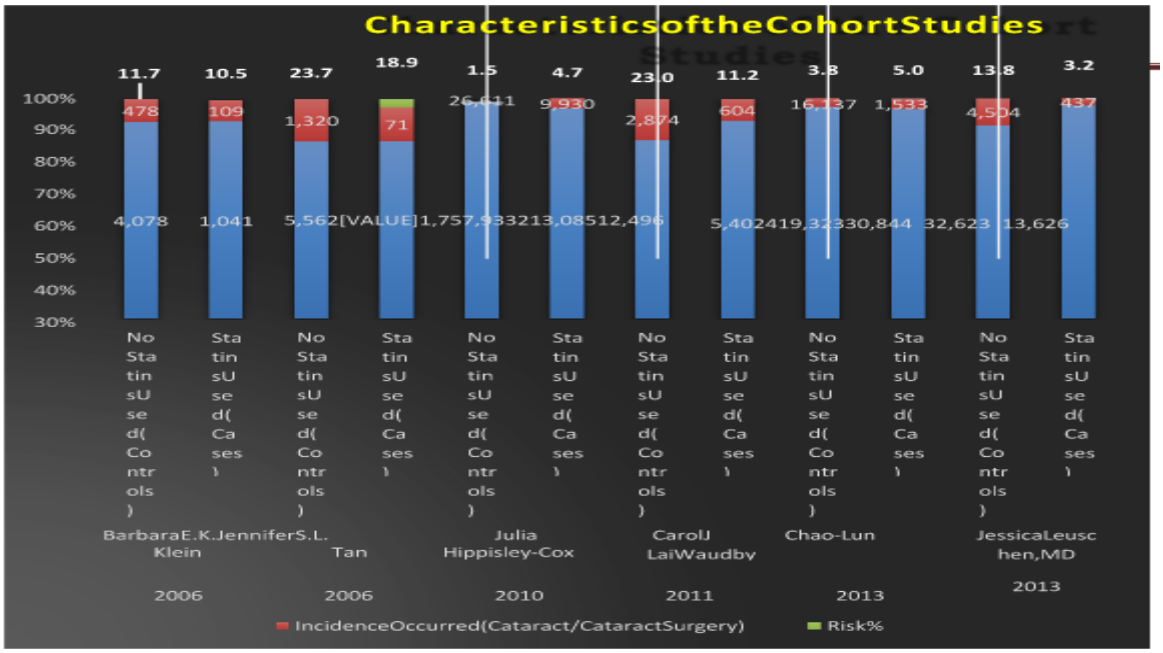

Figure2

Table3:CharacteristicsoftheCase–ControlStudies

PublishedYear	Author	No.ofsubjects		IncidenceOccurred(Cataract/Cataract Surgery)	Risk%
2001	RG Schlienger	No Statins Used(Controls)	28,327	831	2.9
		StatinsUsed(Cases)	7,405	218	2.9
2003	L.SMEETH	No Statins Used(Controls)	15,479	293	1.9
		StatinsUsed(Cases)	15,479	403	2.6
2012	Donald SFong	No Statins Used(Controls)	34,049	18,893	55.5
		StatinsUsed(Cases)	13,583	8,739	64.3
2014	StephanieJWise	No Statins Used(Controls)	650,004	11,490	1.8
		StatinsUsed(Cases)	162,501	1,952	1.2
2014	JayC Erie	NoStatinsUsed (Controls)	2,038	34	1.7
		StatinsUsed(Cases)	2,557	32	1.3

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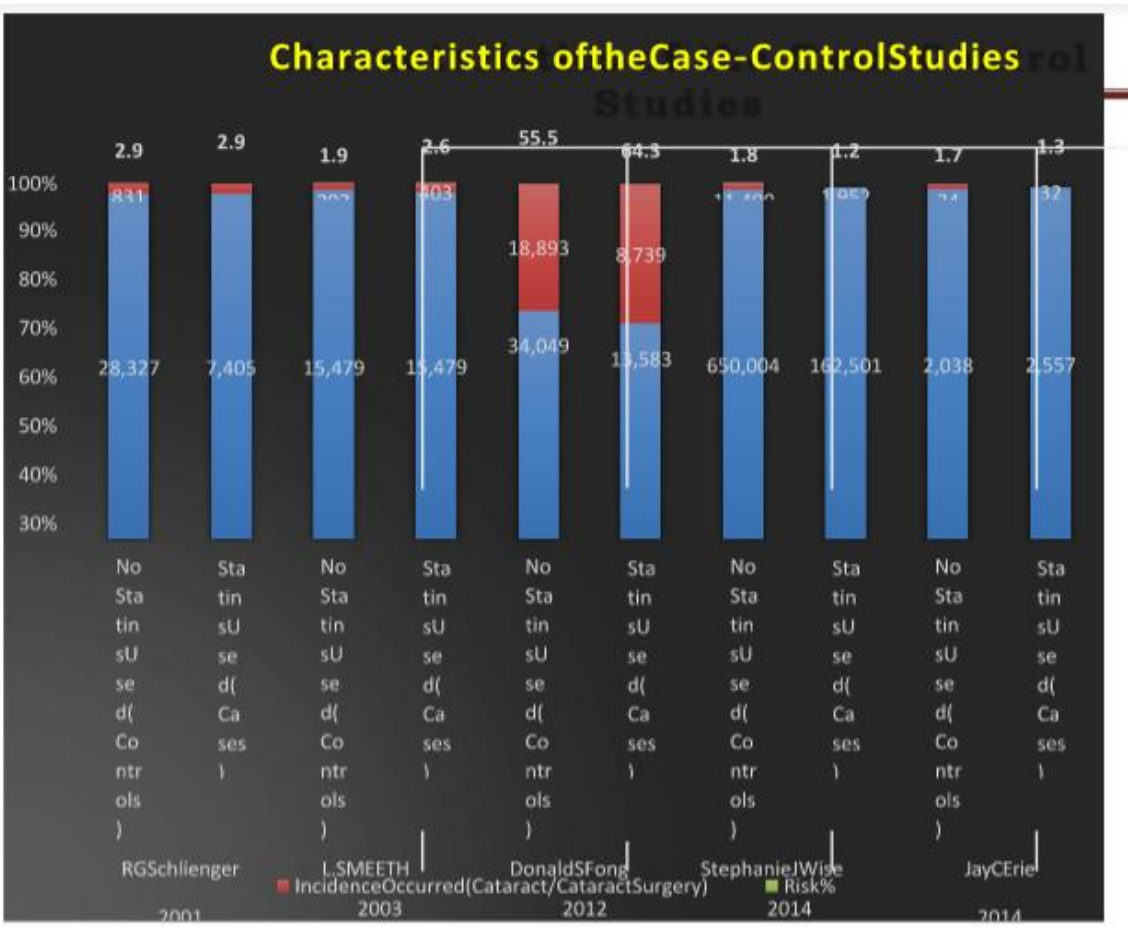

Figure3

Table4:CharacteristicsoftheRCTs

PublishedYear	Author	No.ofsubjects		IncidenceOccurred(Cataract/CataractSurgery)	Risk%
2002	Lancet	NoStatinsUsed (Controls)	10,267	1,507	14.7
		StatinsUsage(Cases)	10,267	1,328	12.9
2015	Casper NBang	No Statins Used(Controls)	1,873	0	0.0
		StatinsUsed(Cases)	1,873	65	3.5

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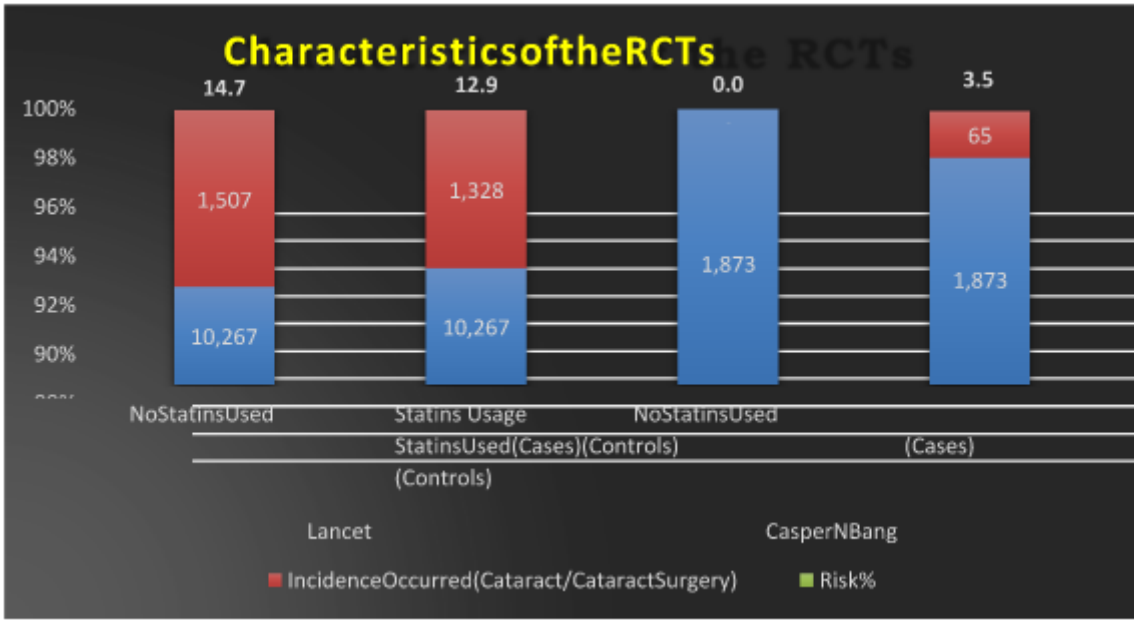

Figure4

Inthiscomprehensivemeta-analysisof6 cohort, 6 case– controlstudies, and 5 RCTs, we analysed the effect of statin use on the risk ofcataracts in more than 313 200 patients. Analysis of the cohort studiesshowedthatstatinusewasassociatedwitha 13%increasedriskofcataracts.

However, analysis of the case–control studies and RCTs revealed noassociation between statin use and the risk of cataract. The effect sizeof the case–control studies was marginal, namely, RR=1.10 (95% CI,0.99–1.23).Basedonthedifferingcharacteristicsofobservational(case–control and cohort) studies and RCTs, such discordant resultsarenotunexpected.Becauseoftherigorouscriteriaof RCTs,individualsatgreatestriskforadverseeventsmaybeexcluded.Furthermore, the subjects of RCTs may be healthier than the subjectsofobservationalstudies.

TheRCTsinthisanalysishadgoodinternalvalidity,buttheexternalvalidity was limited. The conclusion could not be extended to the wholepopulation.Inapopulationsimilartothestudypopulation, theconclusionwasreliable.Moreover,theremaybealargeportionofpatientssimilartothepatientsenrolledintheseRCTs.However,thereare also many patients who are not similar to the patients enrolled inthese RCTs. The observational studies involve more cases with differenthealthconditions.However,inobservationalstudies,baselineconfounderscanbepresent, whichmayaffectthe results. In suchstudies,relativetonon–statinusers,statinusersmaybeexpectedtobe of poorer health or to have higher risk factors that necessitate statintherapy.Asaresult,adverseeventratesmaybehigheramongstatinusers.Althoughmostobservationalstudies(includingthepresentmeta-analysis)haveattemptedtocharacterizetheirpatientsandidentifyvalidatedmarkersofmorbidityandmortality,potentialunidentifiedconfoundersmayexist.35,36Thismayleadtoacalculated effect size that is slightly higher than the real one. Therefore, the realeffectmaybenosignificantassociation.

Theanalysesofcohortandcase–controlstudieswerelimitedbytheconsiderable heterogeneity across studies. In the subgroup analysis ofcohortstudies,theI2valuesdecreasedsignificantlywhensubgroupedbysex,outcomeassessment, age,follow-up duration, or consultationrateincluded/missingmodel(Table S5,FiguresS6, S7, S9, S10, andS14).Inthefemale(FigureS6B),noolderthan60years(FigureS9B),and less than 5 years follow-up subgroups(Figure S10B), the I2 valuesdecreasedbecausetheweightofCox'sstudywasmuch higher (morethan70%).Intheconsultationrateincluded

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modelsubgroup(FigureS14A),theI2valuedecreasedbecausetheweightofLai's study wasmuch higher (more than 80%). Consequently, the heterogeneity may bepartlyattributedto the outcome assessment. The evaluation criterionofvariousassessmentmethods may have varied among the studies,andpatientsdiagnosedwithcataractsby1 methodmaynotbesodiagnosed when another method is used. Further more, even when thesamemethodfordiagnosisisused,differentphysiciansmaymakedifferentdecisions,especiallyregardingcataractsurgery. In thesubgroupanalysisofcase–controlstudies,theI2 values weresignificantly decreased when sub grouped by quality assessment, studylocation,typeofstatin,CVDincluded/missingmodel,smokingincluded/missingmodel,consultationrateincluded/missingmodel,orhypertensionincluded/missing model (Table S6, Figures S16, S17,S19,S21,S22,S23,andS25).In the quality assessment andhypertensionincluded/missingmodelsubgroups,theI2valuesofthehigh-quality group (Figure S16A) and the hypertension missing model(FigureS25B)decreasedbecausetheweightsoftheWise-IMSstudy(more than 95%) and the Fong study (more than 70%) were much higherthan those of the other studies. In the subgroup analyses of the studyperformedinEurope(FigureS17B),theCVDmissingmodel(FigureS21B), and the consultation rate included model (Figure S23A), the I2values decreased because the included studies were derived from thesamedatabase.Therefore,the heterogeneity may be partly attributedtothetypesofstatins.Statinshaveextensivepleotropiceffects thatextendbeyondtheircholesterol-loweringproperties.35,37Differenttypesofstatinsmayaffectcataractdevelopmentby differentmechanisms.Therefore,patientstaking differentstatinsmayhavedifferentrisksfordevelopingcataracts.Inoursubgroupanalysisbasedonstatintype,theI2valuesoffluvastatinandpravastatinweresignificantlydecreasedcomparedwiththatoftheoverallresult(FigureS19).Furthermore,the doseofstatinsalsodiffered amongstudies. In addition to the fact that these factors may contribute to theheterogeneity,someotherfactors,suchasethnicity,14ultravioletexposure,andeducationlevel, may also lead to heterogeneity.38–40Thedifferenceintheascertainmentmethodofstatinusewasalsoasource of heterogeneity. Klein et al15 and Tan et al16 determined statinuse according to patient interviews, whereas in other studies, statin usewasascertainedaccordingtocomputerizedprescriptionrecords.12–14,17–22 However, even if prescription records or interviews showedthat a patient was prescribed statins, differences in patient compliancemayhaveresultedindifferentdegrees ofexposure,whichmayhaveledto heterogeneity. Some previous studies have found that statin use hasdifferenteffectsondifferenttypesofcataract;35,37therefore,heterogeneity may result from study variations in the types of cataractand the proportions of statin types used.Two of theincluded studiesreported that statin use was protective against cataracts.15,16 These 2studies are long-term prospective cohort studies that followed patientsusingperiodicallensphotographs.Such a design tends to achievereliable results. However, these studies had limitations. The rate of losstofollow-upwasrelativelyhighinthese2studies(morethan20%atthe 5th year).15,16 Moreover, the sample sizes of these 2 studies wererelativelysmall.

The analysis of the RCTs indicated that statin use does not increase theriskofcataract.Most ofthe individualresultsofincludedstudies areconsistent with this overall result. In the subgroup analyses by age andfollow-up duration, no association was observed between statin use andcataractrisk(TableS7).TheSEASstudyreportedthatpatients withaortic stenosis that were treated with simvastatin and ezetimibe had alower risk of cataract than did patients treated with placebo.27 Becausethe treatment group received ezetimibe, which is a cholesterol-loweringagent, this result may be overlooked in this study.41 Heterogeneity mayhavealsoarisenfromthisstudy.

Thestrengthsofourmeta-analysisincludetheanalysisofbothobservational studiesandRCTsandthelargesamplesize.Despiteitsstrengths,there are several limitations of our analysis. First, evidenceofamong-studyheterogeneityofthe observational studies wasapparent. Although we performed subgroup analyses in an attempt toidentifythesourcesofheterogeneity,thesevaria

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blescouldnotfullyexplaintheobservedheterogeneity,suggestingthatotherunknown,confoundingvariablesmightberesponsible.Second,theconfoundingfactorsvariedamongtheincludedstudies. BecauseofthelimitationsofobservationalstudiesandRCTs,large,multicenter,pragmatic,prospectiveobservationalstudiesorregistriesshouldbeperformedinthefuturetoassesstheriskofcataracts.The

primaryendpointsshouldincludenotonlycardiovasculardiseasesbutalso totalcomorbidity.Moreover,patientsshouldbestratifiedaccording to baseline confounders. Cataracts should be confirmed byobjective serial testing using validated tools, and per-protocol analysisshould be used to determine the protocol effects on results. Finally,investigators should attempt to characterize and follow the outcomes ofthosepatientswhodropoutofthetrials. Basedonthepresentmeta-analysisofthesestudies,wecould only conclude that there is no clear evidence showingthat statin use increases the risk of cataract. The most likelycaseisthatthereisnoassociation.Because oftheconsiderable benefits of statins in cardiovascular patients,thisissueshouldnotdetertheuseofstatins.

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