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

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I. INTRODUCTION

Astatinisa class of drugs that are mainly used to lower cholesterol levels in the body. Statin drugs work by blocking the action of a certain chemical found in the liver that makes cholesterol. We all need some level of cholesterol in our bodies. Cholesterol is required for our cells to function correctly. Statins have shown promise as antihypertensive drugs because of their ability to lower both diastolic and systolic blood pressure. The mechanism by which statins act to reduce blood pressure is unknown.

Statins, also called HMG-CoA reductase inhibitors, are drugs that act to lower cholesterol levels by inhibiting the enzyme HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which is required for cholesterol synthesis. Examples of statins include simvastatin, pravastatin, and lovastatin. Statins are generally quite safe, but side effects may include muscle pain and fatigue. A rare side effect called myopathy, characterized by muscle degeneration, has been associated with mutation in the gene involved in mediating liver uptake of statins. Cataracts are the main cause of low vision and blindness worldwide. Nearly 13 million people in the United States are reported to suffer from cataracts.

Types of statins:

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

Statins are a main cause of poor vision; with the growing elderly population, the incidence of cataracts is likely to increase. Investigators have previously hypothesized that statin antioxidant effects may slow the natural aging process of the lens. There is mounting evidence that statins are beneficial to a wide range of people at risk of cardiovascular disease. Increasing recognition of the beneficial effects of statins, combined with the expiry of drug patents for some of the earlier statins, means that the use of statins is likely to increase markedly, particularly in the developing world, where cataract is the leading cause of blindness. Acetactisclaudingoftheeye's lens. Cataract is the leading cause of blindness among people older than 55. Most older people have some degree of lens clouding, which is a normal part of aging. Cataracts are generally painless. They usually start out as a small, opaque spot and slowly grow larger. They can affect the development of cataracts. However, researchers have pointed out that the relationship is not conclusive and by no means shows a cause-and-effect relationship. However, researchers have stated that patients who use statins may be at an increased risk for developing cataract.

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ness, specifically for the elderly,” said lead investigator Dr. Isha Mansi, of the VA North Texas Health System in Dallas. “This study confirmed that statin use is associated with a higher risk of being diagnosed with cataract; rather, it identifies statin use as associated with a higher risk of developing cataracts compared with non-users, where researchers found. It is estimated that one in four Americans over age 45 currently takes a statin. In November 2013, the American College of Cardiology and the American Heart Association jointly announced new treatment guidelines for high cholesterol that likely will double the number of statin users. Such a significant increase in statin use makes it even more important to understand the role of cholesterol-lowering statins, which are taken by millions of people around the globe to lower triglyceride levels, and even though cataracts may develop as a result of taking life-saving medication, they are treatable. In fact, the National Institutes of Health say that procedures to repair cataracts are among the most common and safest surgeries performed in the U.S. This surgery removes the old, clouded lens from the eye and replaces it with a new, artificial one to restore the patient’s vision. A nationwide cohort study led by researchers at Wilford Hall Ambulatory Surgery Centre, in San Antonio, Texas, and funded by the US National Institutes of Health looked at a large cohort of 6,972 pairs of statin users and non-users, comparing the risk of developing cataracts between the two groups. The results, published in the Journal of the American Medical Association (JAMA), found that about a third of both statin users and non-users developed cataracts during the study period, although the risk was slightly higher for the latter. However, a separate analysis by the same team suggested that the risk of cataracts could be much higher in those taking statins for primary prevention (i.e., in patients at risk from cardiovascular disease who have not yet suffered a related event, such as a heart attack). This analysis compared 6,113 healthy statin users (with no comorbidities) with 27,400 non-takers. After adjusting for various factors, including demographic characteristics, medications, and health care use, it was concluded that 34% of statin users were diagnosed with cataracts versus 10% of those not taking cholesterol-lowering medication. This is not the first time a link between cataracts and statins has been indicated, though prior research into the relationship has not been consistent. In addition, the study did not factor in whether the type of statin or dosage had any effect on the risk. Nevertheless, the researchers stressed that “the risk-benefit ratio for statin use, specifically for primary prevention, should be carefully weighed,” and have called for further studies to better determine the relationship between their use and cataract development. The benefits of statins are outweighed by any small risk for surgery. The development of age-related nuclear cataract might be associated with oxidative stress. As statins have antioxidant effects, they might diminish the incidence of age-related nuclear cataract. Klein and colleagues, therefore, investigated whether statin use reduced the risk of incident age-related nuclear cataract in a longitudinal, population-based study. This meta-analysis aimed to explore the preventive effects of combined statin and antihypertensive therapy on major cardiovascular outcomes in patients with hypertension. PubMed, Embase, and the Cochrane Library databases and reference lists of published studies were systematically searched throughout October 9, 2019. Studies designed as randomized controlled trials and investigating the effects of combined statin and antihypertensive therapy versus antihypertensive therapy alone were included. Data abstraction and quality of included studies were assessed by two independent authors. The summary results were calculated using relative risk (RRs) with 95% confidence intervals (CIs) using a random-effects model. A total of 8 randomized controlled trials including 38,618 patients were finally enrolled. The summary RRs indicated that the combined therapy significantly reduced the risk of major adverse cardiovascular events compared with antihypertensive therapy alone (RR0.79; 95% CI0.71–0.88; p<0.001). Furthermore, the patients in the combined therapy group also experienced less myocardial infarction.
ardialinfarction (RR0.67; 95% CI0.53–0.84; p=0.001) and stroke risks (RR0.82; 95% CI0.72–0.94; p=0.005), while no significant differences were observed between combined therapy and antihypertensive therapy 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). These findings suggested that combined statin and antihypertensive therapy was associated with more cardiovascular benefits compared with antihypertensive therapy alone. High blood pressure is more frequently observed in individuals aged more than 25 years, affecting more than 40% of adults worldwide. It is the leading cause of death or disability. The American Society of Hypertension collaboration group in 2009 defined hypertension as a progressive vascular syndrome caused by a series of complex and interwoven factors, evidenced by an increase in blood pressure. Furthermore, hypertension is considered a traditional risk factor for cardiovascular disease (CVD) risks when combined with other cardiovascular risk factors. However, the residual risk of cardiovascular outcomes remains high owing to patients having various cardiovascular risk factors. Therefore, combined statin and antihypertensive therapy, even in olypills, should be used according to risk factors, including antihypertensive treatment and combined statin therapy. The absolute risk of cardiovascular outcomes, which can yield greater cardiovascular benefits compared with the treatment strategy based on a single risk factor. Statins are used as common lipid-lowering drugs globally for preventing CVD. Recently, a synergistic effect of combined statin and antihypertensive therapy contributed to the prevention of CVD progression. However, evidence supporting the use of statins combined with blood pressure-lowering medications for treating patients with grade 1 hypertension, irrespective of cholesterol levels, is lacking. Patients with hypertension present in the moderate-risk category should be treated with statins. Moreover, lifestyle interventions should be implemented to lower blood pressure and improve quality of life. However, studies reporting inconsistent results regarding the effect of combining statin and antihypertensive therapy on major cardiovascular outcomes. This might be because recruited patients did not “purely” have hypertension, which always combined with other cardiovascular risk factors. In previous meta-analyses, combined statins and intense blood pressure-lowering regimens were compared. The outcomes of the intervention suggest a benefit of combined statin and antihypertensive therapy on major cardiovascular outcomes. Therefore, this systematic review and meta-analysis based on the available randomized controlled trials (RCTs) was conducted to evaluate and compare the effects of combined statin and antihypertensive therapy. 

II. LITERATURE REVIEW

Dan Cook 2018: Statin use was significantly associated with the development of cataracts in two distinct older patient populations, according to new findings. The study touched on an important issue in the treatment of the elderly, who are commonly prescribed statins to manage cardiovascular disease (CVD), but who also demand acceptable vision throughout their golden years. Investigators used the British Columbia Ministry of Health database to assess 62,501 Canadian men and women who averaged 73 years of age at docus statins for at least one year before undergoing cataract surgery and more than 650,000 matched individuals with no history of cataracts. According to the study, the adjusted rate ratio (RR) of cataract formation in patients on regular statin use was 1.27, with an adjusted RR of 1.36 for new users and 1.24 for previous users. The adjusted RR for the long-term use of statins ranged from 1.14 for lovastatin to 1.42 for rosuvastatin. 

Prof. Harry Struijker-Boudier 2017: FESC Statinshavereachedapromi
The original trials in the 1990s that showed the effectiveness of statins in reducing cardiovascular risk in coronary heart disease have been followed up by long-term safety and efficacy trials. These studies support the wider adoption of statins in primary and secondary prevention strategies. Thereby, the increased understanding of the role of statins in cardiovascular risk, the use of a statin should be considered in hypertensive patients. However, the individual decision to use a statin should be based upon individualized estimates of risk reduction and adverse effects.

Abdullah Nassief MD 2008: Statins are widely used to reduce the risk of stroke in patients with coronary artery disease (CAD), but less so in patients without CAD. We reviewed recent trials for new evidence for the reduction in risk of stroke. In patients with CAD, moderate-intensity statin 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 compared with moderate-intensity lipid lowering in patients with stable CAD. Evidence is now available that the therapy also reduces stoke risk in patients without CAD by reducing cardiovascular risk, or with diabetes mellitus. The SPARCL trial showed that intensive statin therapy started within 6 months after a cerebrovascular event significantly reduced stroke risk and stroke severity.

L Robman & H Taylor 2005: Age and heredity are the most important risk factors associated with the different types of cataract. While the hereditary component is self-explanatory, the increasing age serves as an asurrogate for a number of potential external risk factors. The effect of which is cumulative. Identification of other risk factors that have a causal effect on cataract development may provide means for cataract prevention. There are many factors that have a causal effect: smoking, which results in the increased risk of nuclear cataract, excessive UV-B exposure and diabetes that increase the risk of cortical cataract, and steroid and ionising radiation that lead to the formation of posterior subcapsular opacity. The effect of medications on cataract development requires further study, since the effect of the disease is not determined by smoking or steroid use.

Phelan and Link 2005: In this study, we examine how income gradients in cholesterol level have changed with the emergence of statins (or HMG-CoA reductase inhibitors). Though cholesterol was recognized as an important risk factor for cardiovascular disease as early as the 1960s, it was not until the 1990s that intensive lipid lowering became widespread. The TNT trial, which showed a reduction in stroke risk, was a landmark study. Since then, a number of studies have confirmed the benefits of statins in reducing cardiovascular risk.

Griffiths(2002): Amini-review double-blind randomized controlled trials (RCTs) was used in the study. The results show that statins may reduce the risk of stroke and myocardial infarction. However, further research is needed to confirm these findings.
dertakentoassessthelong-term effect oflipid-lowering treatments (statins versus placebo) in secondary prevention of myocardial infarction (MI). The population sample was adult patients with a history of MI, documented tendonary heart disease or coronary artery disease. The Cochrane Library and the database Medline were searched and three RCTs appeared to possess all the stipulated inclusion and exclusion criteria. Thetria Isall compared statins against a placebo; one trial was of simvastatin—the Scandinavian Simvastatin Survival Study (1994)—and the other two were of pravastatin—the Cholesterol and Recurrent Events Trial (CARE) (Sacks et al., 1996) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) (Anon, 1998). The trials demonstrated that statins had a clear and consistent effect in significantly reducing the risk of MI. Overall, an approximate decline of 30% in MI was produced from the three trials.

Newman et al.: Performed a rigorous examination of the safety and tolerability of statins as a class, highlighting differences among the agents as appropriate. Utilizing data from randomized controlled trials, supplemented with observational data, this review covered both subgroups potentially vulnerable to adverse events including the elderly, children, pregnant women, and East Asians. Italsodiscussed treatment of patients with chronic kidney disease, HIV, and those undergoing organ transplantation. This commentary is meant to clarify and highlight the salient clinical practice lessons we feel both primary and specialty providers should be aware of.

Virmani et al., 2000: An atherosclerotic plaque is characterized by trimming of the fibrous cap that is infiltrated by macrophages and T cells with few SMCs, and an increase of extracellular lipids and necrotic core formation. Such plaques are vulnerable to rupture, thereby evoking atherothrombosis, myocardial infarction, and stroke. Several authors have been proposed to increase the risk of plaque rupture, such as increased collagen degradation by matrix metalloproteinases secreted by macrophages, or decreased collagen biosynthesis because of suppression of SMC activity by interferon-γ, acytokine produced by T cells. Clarke et al., 2006). SMC death is seen in the vicinity of macrophage-rich regions of human atherosclerotic plaques (Kockx et al., 1996, 1998). Factors that are known to kill SMCs can be macrophage derived (nitric oxide (NO), Fas ligand and tumour-necrosis factor-α) or products formed during oxidative modification of lipoproteins and cholesterol. Indeed, oxysterols such as 7-ketocholesterol, may induce necrosis (Ghelli et al., 2002; Seye et al., 2004), apoptosis or type I cell death (Lizard et al., 1996, 1997; Seye et al., 2004) or autophagy (Martinet et al., 2004) in vascular cells. Autophagic type II cell death is a caspase-independent form programmed cell death (Gozuacik and Kimchi, 2004; Ferrarao and Cecconi, 2007). Processing of microtubule-associated protein light chain 3 (LC3) from the cytoplasmic form (LC3-I) to the membrane-associated form (LC3-II) is essential for the formation of autophagosomes with autolysosomes increased electrophoretic LC3 mobility on SDS-polyacrylamide gels (Gozuacik and Kimchi, 2004; Ferrarao and Cecconi, 2007).

Lynch, 2003; Pappas et al., 1993: In a seminal article published over a decade ago, Link and Phelan (1995) argued that social factors such as SES can operate as persistent and “fundamental causes of disease” because they are associated with a wide variety of resources that can be marshaled to improve health in diverse environments. To date, however, there have only been a few examples of empirical support tests of the theory, and they have generally focused on whether SES gradients in mortality are strong er for causes of death that are considered more preventable, indirectly assessing the role of resources in improving potential interventions.
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**Dr. John B. Kostis:** The bottom line is that statins prevent cataracts,” said Dr. John B. Kostis during a presentation at the annual congress of the European Society of Cardiology. “But the bottom line is: Don’t be scared of cataracts when prescribing statins.”

Dr. Kostis noted that statins were approved by the Food and Drug Administration with the precaution that patients should be examined with a slit-lamp before and during treatment.

**Dr. WILLIAMS:** There was also a 1.4% absolute risk reduction (P less than 0.0001), demonstrating that 71 individuals needed to be treated with statins to prevent one case of cataracts. Meanwhile, patients who began statin therapy in their 40s had a 51% lower chance of cataracts (OR, 0.49), compared with those who began the treatment in their 70s and probably already had cataracts (OR, 1.03, or nonrisk reduction), he said. “It is possible that these processes (aging and statins) work in parallel or interactively,” Dr. Kostis said in a news release. In addition, there was a 46% reduction in the risk of cataracts when patients were treated with statins for as long as 14 years (OR, 0.54), compared with a 10% risk reduction among those who were retreated for only 6 months (OR, 0.90). Gender did not play a role in the findings. The meta-analysis had several limitations. Each of the studies had a different design, and the randomized clinical trials didn’t have cataracts as an endpoint. Also, the certainty of exposure to statins in observational studies is imprecise, and there is the possibility of reporting and publication bias, Dr. Kostis noted. The strength of the meta-analysis was in the consistency of the statins’ effect when it was analyzed from various aspects, he said. In addition, all published reports on the topic were included in the analysis. Moreover, the effect of statins in preventing cataracts was significantly more pronounced for the hard endpoint of cataract extractions.

A large, randomized clinical trial could put the uncertainty to rest, noted Dr. Kim Allan Williams Sr., chair of cardiology at Wayne State University, Detroit. But the findings from this analysis were reassuring, added Dr. Williams, who was not involved in the meta-analysis.

**M. MYOSH:** Sphingosine 1-phosphate (S1P) is a cationic metabolite and is present in submicromolar concentrations in normal human sera (Yatomi et al., 1997). Recent studies have revealed that this lipid is capable of modulating a very wide variety of biological activities in numerous organs in mammals (reviewed in Hla, 2003). Specifically, in vascular endothelial cells, S1P mediates important effects such as migration, survival, proliferation, vasorelaxation and angiogenic morphogenesis (Hla, 2003). Many of these effects of S1P are mediated by its binding to and activation of G-protein-coupled S1P receptors, which are expressed at the endothelial cellsurface (reviewed in Hla, 2001). Five independent receptor subtypes, S1P1–S1P5, have been identified in mammals, of which S1P1 and S1P3 represent major receptors for S1P in vascular endothelial cells (Lee et al., 1999; Morales-Ruiz et al., 2001). Effector molecules that mediate S1P receptor activation to physiological responses of vascular endothelial cells include the endothelial isoform of nitric oxide synthetase (eNOS), which in turn is modulated by its upstream protein kinase cascades, phosphoinositide 3′-OH kinase (PI3-K)-Akt (Igarashi et al., 2001a, 2001b, 2003). Interestingly, S1P, which was found to be enriched in high-density lipoprotein (HDL) fractions of normal human sera, may play key roles in mediating HDL-induced vascular endothelial responses (review ed in Okajima, 2002). Thus, alterations in expression of S1P1 receptors could potentially influence the responses of...
vascularendothelialcellstoserumlipoproteinc onstituents.anvascularendothelial cells, expression levels of S1P1 receptors are subject todynamic regulation by extracellular stimuli, including phorb esters(Hla and Maciag, 1990) as well as vascular endothelial growth factor(VEGF) (Igarashi et al., 2003). It seemed therefore plausible to us thatstatinsmightmodulate S1P1receptorexpressionlevelsandsubsequent sphingolipid signaling of endothelial cells. In the presentstudies, we provide evidence that statins increase expression levels of S1P1 receptors and augment eNOS responses to S1P as well as to HDLinculturedvascularendothelialcells.

PETER DHiggins: Randomized controlleddr ials for preventing cardiovascular diseaseindica tedthatstatins had a provacative and unexpected benefitsonreducing colorectal cancer and melan oma. These findings have led to the intensivestud y of statins in cancer prevention, including recent, large population-based studies showingstatin- associated reductions in mortality, colorectal and prostate cancer. Understanding the complexcellulareffe cts (forexample, onangiogenesis and inflammation) and the underlying molecular mechanismssof statins (forexample, 3-hydroxy-3- methylglutarylcoenzyme-A (HMG-CoA) reductase-dependent processes that involvegeranylgeranylationofRhoproteins, an d HMG-CoA-independent processes that involve lymphocyte-function-associated antigen 1) will advance the development of molecularly targeted agents for preventing cancer. This understanding might also help the development of drugs for other ageing-related diseases with interrelated molecular pathw ays.

BA De Waal, MP Buise, AAJ Van Zundert: Statins feature documented benefits for primary and secondary prevention of cardiovascular disease and are thought to improve perioperative outcomes in patients undergoing surgery. To assess the clinical outcomes of perioperative statintreatment in statin-naive patients undergoing surgery, a systematic review was performed. Studies were included if they met the following criteria: randomized controlled trials, patients aged ≥18 years undergoing 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 hospital stay. The following randomized clinical trials were excluded: retrospective studies, trials without an outcome of interest, studies with patients on statin therapy before operation, or papers not written in English. The literature search revealed 16 randomized controlled studies involving 2275 patients. 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) perioperative atrial fibrillation (RR 0.53, 95% CI 0.43–0.66, P<0.001), and (iv) length of hospital stay (days, mean difference −0.58, 95% CI −0.79 to −0.37, P<0.001) in patients treated with a statin. Subgroup analysis in patients undergoing non-cardiac surgery showed a decrease in the perioperative incidence of mortality and myocardial infarction. Consequently, anaesthetists should consider prescribing a standard-dose statin before operation to statin-naive patients undergoing cardiac surgery. However, there are insufficient data to support final recommendations on perioperative statin therapy for patients undergoing non-cardiac surgery.

Marcus M Reidenberg: The painful or tender myopathy with elevated CPK due to statin drugs is well described and uncommon [1, 2]. Statin myopathyno can also occur with elevated C PKorpain [3, 4]. More common is a feeling of lack of energy in people taking these drugs. Sinc estatin induced malonyl CoA reduction[5], the lowerlevelsofubiquinone, an essential compound for mitochondrial energy production, as well as lowering cholesterol. Thus, these people may truly lack energy. A few people who described lack of energy or having aged rapidly while on statins were advised to take ubiquinone (co-enzyme Q10, Co-Q10) while continuing the statin. Their energy level improved and they felt better.
blind trial comparing 35 mg Co-Q10 bid with placebo bid was initiated after approval by the Weill Cornell IRB for patients on statins who felt lack of energy since starting the statins and who did not have muscle pain, tenderness, or elevated CPK. By the time this trial started, most patients in my geographical area with these symptoms either stopped the statin or started Co-Q10 on their own, thus only three subjects were accrued in 1.5 years and the trial was stopped. The subjects’ ages were 68, 69, and 75. Plasma Co-Q10 levels were measured by sample pretreatment with 1,4-benzoquinone to change the reduced form of Co-Q10 to the oxidized form, precipitation with 1-propanol, and assayed by HPLC with redox electrical chemical detection in the laboratory of Dr. MF Beal [6,7].

Fatima Mraiche, Jonathan Cena: Although statins have been reported to inhibit the prepro‐endothelin‐1 (ET‐1) gene transcription in endothelial cells, their effects on the vascular function of ET‐1 have not been explored. We, therefore, examined the effects of statins on contraction and DNA synthesis mediated by ET‐1 in vascular smooth muscle. The effects of statins on contraction induced by ET‐1 were compared to those mediated by noradrenaline (NA) and KCl. Simvastatin (SV) induced a concentration‐dependent relaxation of tonic contraction mediated by ET‐1 (10 nm) (IC50 value of 1.3 μm). The relaxation was also observed in rings precontracted with NA (0.1 μm) and KCl (60 mm). In contrast, pravastatin did not have any effect on the contractions. 3 Endothelial denudation or pretreatment with l‐NAME did not prevent the relaxation, but did reduce the relaxant activity of SV, while pravastatin maintained the relaxation of aortic homogenates, as assessed by a Rho pulldown assay. 5 The Rho kinase inhibitor HA1077 mimicked the effects of SV on tonic contractions induced by ET‐1, NA, and KCl.

Mehboub Ahmed: Amini‐review (Griffiths, 2002) of double‐blind randomized controlled trials (RCTs) was undertaken to assess the long‐term effect of lipid‐lowering treatments (statins versus placebo) in secondary prevention of myocardial infarction (MI). The population sample was adult patients with a history of MI, documented coronary heart disease or coronary artery disease. The Cochrane Library and the database Medline were searched and three RCTs appeared to possess all the stipulated inclusion and exclusion criteria. The trials all compared statins against a placebo; one trial was of simvastatin – the Scandinavian Simvastatin Survival Study (1994) – and the other two were of pravastatin – the Cholesterol and Recurrent Events Trial (CARE) (Sacks et al., 1996) and Longterm Intervention with Pravastatin in Ischaemic Disease (LIPID) (Anon, 1998). The trials demonstrated that statin‐shadaclear and consistent effect in significantly reducing the risk of MI. Overall an approximate decline of 30% in MI was produced from the trials.

HALBERTL. WHITE: We performed a randomized, double‐blind, placebo‐controlled trial with equal allocation to simvastatin, 20 mg; pravastatin sodium, 40 mg; or placebo for 6 months. Nine hundred seventy‐three men and women without known cardiovascular disease or diabetes mellitus, with low‐density lipoprotein cholesterol screening levels of 115 to 190 mg/dL, had assessment of systolic and diastolic BP (SBP and DBP, respectively). Blood pressure values were compared for placebo vs statins by intention‐to‐treat (ITT) analysis. Additional analyses were performed that (1) were confined to subjects with neither high baseline BP (SBP > 140 mmHg or DBP > 90 mmHg) nor receiving BP medications, and (2) separately evaluated simvastatin and pravastatin (vs placebo). The time course of BP changes after statin initiation and the effect of stopping statins on BP were examined. Reductions in SBP and DBP occurred with hydrophilic and lipophilic statins and extended from normotensive subjects. These modest effects may contribute to the reduced risk of stroke and cardiovascular events reported on statins.

Dharani Yerrakalva, Simon J Griffin: The National Institute for Health and Care Excellence (NICE) guidelines on lipid modification advise...
ffering statins for primary prevention to patients with over 10% 10-year modelled risk of a cardiovascular event, a change from 20%. This has generated controversy among clinicians, researchers, and journal editors. Patients already taking statins were more likely to stop taking them after the intense media coverage between March and October 2014, though there was no associated change in initiation. Clinicians’ worries were crystallised in a letter of concern from leading UK medical figures to NICE concerning the frequency of adverse events and the magnitude of the effectiveness of statins. Two sources of evidence were cited regarding risk levels, the meta-analyses by the Cholesterol Collaboration Trialists (CTT) Collaboration and Cochrane.

KJ Gash, ACC Chambers, DE Cotton, AC Williams, MG Thomas: Complete tumour response (pCR) to neo-adjuvant chemoradiotherapy for rectal cancer is associated with decreased local recurrence and improved disease-free and overall survival, but is achieved in only 20–30% of patients. Drug repurposing for anti-cancer treatments is gaining momentum, but the potential of such drugs as adjuvants to increase tumour response to chemoradiotherapy in rectal cancer is only just beginning to be recognised. A systematic literature research was conducted and all studies investigating the use of drugs to enhance response to neo-adjuvant radiotherapy for rectal cancer were included. 2137 studies were identified and following review 12 studies were extracted for full text review. 9 studies were included in the final analysis. Aspirin, metformin and statins were associated with increased downstaging of rectal tumours and thus may have a role as adjuncts to neo-adjuvant treatment, highlighting a need for prospective randomised controlled trials to determine their true impact on tumour response and overall survival.

Alexandros Briasonoulis, Vikram Agarwal: Inex perimental studies, statins have been shown to lower blood pressure through increased nitric oxide bioavailability and improved arterial compliance. The clinical significance of this effect remains poorly documented.

The authors performed meta-analysis of the effects of statins on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in including prospective and randomized controlled trials of statin therapy. EMBASE and MEDLINE searches for studies in which patients were randomized to treatment with statins plus standard treatment (or placebo) were conducted. Studies that provided data on SBP and DBP values before the initiation of the treatment and at the end of the follow-up period were included. A total of 40 studies with 51 comparison groups examining 22,511 controls and 22,602 patients taking statins were examined. Meta-analyses of statin groups decreased by 2.62 mm Hg (95% confidence interval [CI], −3.41 to −1.84; P < .001) and DBP by 0.94 mm Hg (95% CI, −1.31 to −0.57; P < .001).

Xiaoyu Zhang, Jianzhong Wen, Zhiqiang Zhang: Previous studies have indicated that statins use is associated with risk of dementia, but presented controversial results. Medline, Embase, Web of Science, and the Cochrane Database were searched up to November 2017 to identify the potential relations between statin use and dementia. Thirty-one eligible studies involving a total of 3332, 706 participants with 184,666 incident 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 analysis showed statin use was associated with Alzheimer disease (AD) (RR: 0.81; 95% CI, 0.73–0.89) and non-AD dementia (RR: 0.81; 95% CI, 0.73–0.89) risk decrement. Furthermore, statins use was associated with dementia risk decrement in female (RR: 0.89; 95% CI, 0.80–0.98) and male (RR: 0.88; 95% CI, 0.83–
In addition, a dose–response showed per 1 year of duration of statins use incremental increase was associated with 20% dementia risk decrement (RR: 0.80; 95% CI, 0.73–0.87), and per 5-mg mean daily dose incremental increase in statins use was associated with 11% dementia risk decrement (RR: 0.89; 95% CI, 0.83–0.96). Statins use was associated with dementia risk decrement. The potency and the cumulative duration of statin utilization played critical roles.

Fauchier et al. also provided evidence on antiarrhythmic effect of statins [8], and a number of randomized trials have been published since then. Thus, we aimed to conduct a meta-analysis to evaluate the effect of statin use on the endpoint of incidence or recurrence of AF.

JADAD et al. [30]. The number of events in each trial was extracted on the basis of the intention-to-treat approach. All the analyses on the endpoint of AF were performed at the trial level, and one of the datasets of the individual studies were obtained from sponsoring institutions.

Hodick et al., 16 Schlenger et al., 24 Smeeth et al., 25 Collins and Altman, 18 and Tan et al., 26 we used the weighted average of age-adjusted hazard ratios and the number of cataracts in the comparison groups to calculate the number of cataracts in the active groups. In the study by Have et al., where no opacities were observed in either the placebo or lovastatin group, we entered 1 cataract in each group in order to avoid division by 0 to obtain an odds ratio (OR). 27 The specific statin, type of study (randomized vs observational), duration of follow-up in months, percentage of patients who were men, and average age were recorded. Lovastatin was used in 3 studies, 17, 22, 27 and simvastatin in 4 studies, 19, 23, 28 In 7 studies, more than 1 statin was used, and the data were reanalyzed in the aggregate analysis. The following statins were used in these 7 studies: in the study by Tan et al., simvastatin, fluvastatin, lovastatin, atorvastatin, and pravastatin were reused.

Pedersen et al., cataract was not the primary end point, and the data were derived by the authors in a post hoc analysis. 23 In studies where all pertinent information was not included in the primary publication of the trial, we used other publications from the same study in order to obtain the data. When specific data on the occurrence of cataract were not included in the publications, we contacted the senior author to obtain the requisite information. When the dose of the individual statins used was known, the relative dose was calculated by multiplying the dose used times the relative potency (1 for lovastatin, fluvastatin, and pravastatin; 2 for simvastatin; 4 for atorvastatin; and 8 for rosuvastatin). 29–31 Metaregression of studies with known relative potency was performed. There were no studies using either atorvastatin or rosuvastatin alone.

Dr. Mark Fromer, an ophthalmologist at Lenox Hill Hospital in New York City, said cataracts are very common. "In one's lifetime, the chance of developing a cataract is 100 percent," he said. "The goal is we want to keep you alive long enough to get one, and that's where statins come in," he said. "Statins increase the length of life by decreasing strokes and heart attacks." Cataracts can be treated with surgery that is “quick, painless and 99.9 percent successful,” Fromer said. "So, since you are going to get a cataract anyway, you might as well take your statin -- it's in your best interest.”

Klein BEK et al. (2006) Statin use and incident nuclear cataract. JAMA 295:2752–2758. The development of age-related nuclear cataract might be associated with oxidative stress. As statins have antioxidant effects, they might diminish the incidence of age-related nuclear cataract. Klein and colleagues, therefore, investigated whether statin use reduced the risk of incident age-related nuclear cataract in an international, population-based study. Of the 2,962 participants in the third examination of the Beaver Dam Eye Study cohort, 1,299 had gradable slit-lamp photographs of both eyes, and were considered at risk of developing incident nuclear cataract within 5 years. Over the 5-
year follow-up period, the incidence of nuclear cataract was 12.2% in statin users (17.2% in nonusers). Participants who developed nuclear cataracts were more likely to be older, female, less educated, and had a lower income than those who did not. Statin use was associated with nearly half the risk of developing nuclear cataract. After adjusting for total cholesterol level, smoking, and diabetes, the relationship between statin use and cataract incidence was not significantly altered.

Bang et al. report that randomized treatment with simvastatin plus ezetimibe was associated with a 44% lower incidence of cataracts in the Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS) trial. Meta-analysis including the SEAS trial and previous studies indicates that the statin use is associated with a statistically significant decrease in the occurrence of cataracts. The findings of SEAS confirm the results of four previous meta-analyses, where a significant protective effect of statins was observed in 8 observational studies (odds ratio [OR] 0.81, 95% CI 0.70 to 0.93, p = 0.004), whereas an effect of similar magnitude was observed in the 6 randomized trials but did not reach 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 randomized trials, the effect became statistically significant (OR 0.78, 95% CI 0.63 to 0.95, p = 0.0165). Thus, statin use protects against the occurrence of cataracts clinically and statistically.

Dr. Clyde Yancey, cardiology chief at Northwestern Medicine in Chicago, said the results suggested important evidence favoring drug treatment for older-risk patients, but emphasized that lifestyle approaches including diet and activity should be included. He was not involved in the research. The study used 10 milligrams daily of rosuvastatin, sold as a generic or under the brand name Crestor. The authors of the related editorial said other statins would likely have similar results. Crestor’s maker, AstraZeneca, and the Canadian Institutes of Health Research paid for the study. Yusuf reported receiving grants from both; several co-researchers reported grants and personal fees from the company and other drug makers. The blood pressure drugs were candesartan, sold as a generic and by AstraZeneca; Atacand; and hydrochlorothiazide, a generic diuretic.

Bill Sardi what statins teach is that modern medicine would rather treat everybody to find the one who might benefit, rather than target the high-risk individual. Among adult male patients, the death rate due to cardiovascular disease was not addressed by statins. Therefore, the use of statins in preventing cataracts clinically and statistically is significant and primary to be advocated on a large scale.

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there must be something for the cardiologist to do to earn a living. So we have to find another type of heart attack. That would be the clotting heart attack, something.

**Dear Dr Jha,**

I am unable to imagine rosuvastatin (Crestor) as a divine glory of Vishnu. I am able to envision HOP E-3 as an even more egregious example of a marketing trial than JUPITER, the trial that created the mythology that-CRP quantification alone marks a population that should be treated with Crestor despite normal cholesterol levels. The JUPITER trial leaves legacies of medicalization, of increased equity for AstraZeneca, and of fake high bar for data torturing. I made these points when JUPITER first appeared in the NEJM. Along comes HOPE-3, the same exercise in data torturing but now targeting people declared to have “intermediate risk.” Some 13,000 people were recruited in 228 centers in 21 countries. Statisticians and epidemiologists were hired to tease a tiny reduction in clinical outcomes out of all this heterogeneity in a RCT conducted over the course of 5+ years.

Carlos A. Feldstein, MD

There is considerable evidence that hypertension and dyslipidemia are inter-related metabolically, epidemiologically, and clinically.¹ ². The association of hypertension and dyslipidemia confers a greater increase in cardiovascular risk than would be expected with the risk factor alone.³

With regard to this relationship, a recent analysis of data from the National Health and Nutrition Examination Survey 2003-2004 showed that the prevalence of hypertension was ranged from 23.1% in those without cardiovascular comorbidity to 51.8% in those with cardiovascular comorbidity (in chronic kidney disease: 81.8%; in diabetes: 76.8%; in peripheral artery disease: 73.7%; in coronary artery disease: 73.0%; in congestive heart disease: 71.4%; in stroke: 69%; in metabolic syndrome: 61.5%; in dyslipidemia: 51.8%). In spite of higher rates of hypertension in patients with cardiovascular comorbidities (83.4%-89.3%) than those without these conditions (66.5%), control rates for treatment remained low (23.2%-49.3%).⁴

The remarkable benefit achieved with statins in patients with widerange of cholesterol levels cannot be attributed only to their cholesterol lowering effect alone.

Alexandros Briasoulis MD, Vikram Agarwal MD, MPH, Franz H. Messerli MD

In experimental studies, statins have been shown to lower blood pressure through increased nitric oxide bioavailability and improved arterial compliance. The clinical significance of this effect remains poorly documented. The authors performed a meta-analysis of the effect of statins on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in including prospective and randomized trials of statin therapy. EMBASE search and MEDLINE searches for studies in which patients were randomized to treatment with statin plus usual standard treatment (or placebo) vs usual standard treatment (or placebo) were conducted. Studies that provided data on SBP and DBP values before the initiation of the treatment and from the end of the follow-up period were included. A total of 40 studies with 51 comparisons and 22,511 controls and 22,602 patients were examined.

Kyriakoula Merakou, Anastasia Barbouni

The purpose of this study was to determine whether patients undergoing cataract surgery while listening to meditation music experience lower levels of blood pressure and heart rate. Two hundred individuals undergoing cataract surgery participated in the study. Hundred individuals listened to meditation music through headphones before and during the operation (intervention group) and 100 individuals received standard care (control group). Patients’ stress coping skills were measured by the Sense of Coherence Scale (SOC Scale). Systolic and diastolic blood pressure and heart rate were defined as outcome measures.

Wen‐tong Fang, Hong‐jian Li, Haibo Zhan, Su Jiang

Meta-analysis of randomized, controlled trials with use of statins in incidence or recurrence of AF was performed. The use of statins has been suggested to protect against atrial fibrillation (AF) in some clinical observational and experimental studies but has remained inadequately explored. This study was designed to examine whether statins can reduce the risk of AF.
In elderly patients with previous CV events, the use of statins is recommended by guidelines, whereas the benefit of these drugs in elderly subjects without previous CV events is still debated. Randomized trials comparing statins versus placebo and reporting all-cause and CV mortality, myocardial infarction (MI), stroke, and new cancer onset in elderly subjects (age ≥65 years) without established CV disease were included. In elderly subjects at high CV risk without established CV disease, statins significantly reduce the incidence of MI and stroke, but do not significantly prolong survival in the short-term.

Imad M. Tleyjeh, MD, MSc, Fayaz A. Hakim, MD, Emerging epidemiologic evidence suggests that statin use may reduce other risks of infections and infection-related complications. Our objective was to examine the association between statin use and the risk of infections and related outcomes. We searched several electronic databases from inception through December 2007 for randomized trials and cohort studies that examined the association between statin use and the risk of infections. Data on study characteristics, measurement of statin use, outcomes (adjusted for potential confounders), and quality assessment were extracted.

III. AIM AND OBJECTIVE

Aim: To determine whether statin usage affects the risk of cataracts.

Objectives:
1) Assess the risk of cataracts in patients using statins.
2) Perform subgroup analyses based on study design, type of statin, methodological quality of the study, study location, age, sex, follow-up duration, outcome, and outcome assessment.

Search Criteria
The Cochrane Library, PubMed, and EMBASE databases were searched from January 2000 to January 2022 for English language publications, including abstracts. This search was performed using the following terms: "statins OR HMG-CoA reductase inhibitors OR Simvastatin OR Lovastatin OR Fluvastatin OR Pravastatin OR Rosuvastatin OR Atorvastatin" AND "cataract.”

Inclusion Criteria
Studies were included in this meta-analysis if they meet the following criteria:
1) The study should be a case-control, cohort study, or randomized controlled trial (RCT).
2) Non-statin users should be included in the comparison group.
3) Cataracts and/or cataract surgery should be the outcome.
4) The association between statin use and the risk of cataracts/ cataract surgery should be investigated.

Exclusion Criteria
Studies were excluded if they meet the following criteria:
1) Basic science studies
2) Reviews,
3) Editorials/letters
4) Case reports
5) Studies without comparison groups

Data Extraction and Quality Assessment
Data extraction was performed using the following information was extracted from each study: the last name of the first author, year of publication, study design, country of origin of the population studied, patient characteristics, statin use, information source, exposure ascertainment, risk estimates and corresponding 95% CIs, and covariates adjusted for in the multivariable analyses. For studies that provided more than one risk estimate, we extracted the estimate that was adjusted for the...
Outcomes Assessed

The primary analysis focused on assessing the risk of cataracts and cataract surgery among users of statins. We also performed subgroup analyses based on study design (case–control, cohort, or RCT), type of statin, the methodological quality of the study (high or low), study location (Europe, North America, Asia or Australia), age, sex, follow-up duration, outcome and outcome assessment, and whether potential confounders were included in the adjusting model (e.g., low-density lipoprotein included/missing, cardiovascular disease [CVD] included/missing, smoking included/missing).

By searching the 3 databases, 497 potentially eligible articles were identified. In total, 336 articles were excluded after reading the title and abstract, and the full texts of the remaining 161 articles were evaluated in detail. Of these 161 articles, 17 met our inclusion criteria. 17 studies consisting of 6 cohort studies, 6 case–control studies, and 5 RCTs were included in the meta-analysis and involved more than 3,13200 cataract cases.

Table 1: Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Published Year</th>
<th>Author</th>
<th>No. of subjects</th>
<th>Incidence Occurred</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Barbara E.K. Klein</td>
<td>Nostatin used (Controls)</td>
<td>4078</td>
<td>478</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>1041</td>
<td>109</td>
</tr>
<tr>
<td>2006</td>
<td>Jennifer S.L. Tan</td>
<td>Nostatin used (Controls)</td>
<td>5562</td>
<td>1320</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>376</td>
<td>71</td>
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</table>
### Table 2: Characteristics of the Cohort Studies

<table>
<thead>
<tr>
<th>Published Year</th>
<th>Author</th>
<th>No. of Subjects</th>
<th>Incidence Occurred (Cataract/Cataract Surgery)</th>
<th>Risk%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Barbara E. K. Klein</td>
<td>No Statins Used (Controls) 4,078</td>
<td>478</td>
<td>11.7</td>
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<tr>
<td></td>
<td></td>
<td>Statins Used (Cases) 1,041</td>
<td>109</td>
<td>10.5</td>
</tr>
<tr>
<td>2006</td>
<td>Jennifer S. L. Tan</td>
<td>No Statins Used (Controls) 5,562</td>
<td>1,320</td>
<td>23.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases) 376</td>
<td>71</td>
<td>18.9</td>
</tr>
<tr>
<td>2010</td>
<td>Julia Hippisley-Cox</td>
<td>No Statins Used (Controls) 1,757,933</td>
<td>26,611</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases) 213,085</td>
<td>9,930</td>
<td>4.7</td>
</tr>
<tr>
<td>2011</td>
<td>Carol J. Waudby</td>
<td>No Statins Used (Controls) 12,496</td>
<td>2,874</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases) 5,402</td>
<td>604</td>
<td>11.2</td>
</tr>
<tr>
<td>2013</td>
<td>Chao-Lun Lai</td>
<td>No Statins Used (Controls) 419,323</td>
<td>16,137</td>
<td>3.8</td>
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<tr>
<td></td>
<td></td>
<td>Statins Used (Cases) 30,844</td>
<td>1,533</td>
<td>5.0</td>
</tr>
<tr>
<td>2013</td>
<td>Jessica Leuschens, MD</td>
<td>No Statins Used (Controls) 32,623</td>
<td>4,504</td>
<td>13.8</td>
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<tr>
<td></td>
<td></td>
<td>Statins Used (Cases) 13,626</td>
<td>437</td>
<td>3.2</td>
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Table 3: Characteristics of the Case-Control Studies

<table>
<thead>
<tr>
<th>Published Year</th>
<th>Author</th>
<th>No. of subjects</th>
<th>Incidence Occurred (Cataract/Cataract Surgery)</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>RG Schlienger</td>
<td>No Statins Used (Controls)</td>
<td>28,327</td>
<td>831</td>
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<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>7,405</td>
<td>218</td>
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<td>2003</td>
<td>L. SMEETH</td>
<td>No Statins Used (Controls)</td>
<td>15,479</td>
<td>293</td>
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<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>15,479</td>
<td>403</td>
</tr>
<tr>
<td>2012</td>
<td>Donald SFong</td>
<td>No Statins Used (Controls)</td>
<td>34,049</td>
<td>18,893</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>13,583</td>
<td>8,739</td>
</tr>
<tr>
<td>2014</td>
<td>Stephanie JWise</td>
<td>No Statins Used (Controls)</td>
<td>650,004</td>
<td>11,490</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>162,501</td>
<td>1,952</td>
</tr>
<tr>
<td>2014</td>
<td>Jay C Erie</td>
<td>No Statins Used (Controls)</td>
<td>2,038</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>2,557</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 4: Characteristics of the RCTs

<table>
<thead>
<tr>
<th>Published Year</th>
<th>Author</th>
<th>No. of subjects</th>
<th>Incidence Occurred (Cataract/Cataract Surgery)</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Lancet</td>
<td>No Statins Used (Controls)</td>
<td>10,267</td>
<td>1,507</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Usage (Cases)</td>
<td>10,267</td>
<td>1,328</td>
</tr>
<tr>
<td>2015</td>
<td>Casper NBang</td>
<td>No Statins Used (Controls)</td>
<td>1,873</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins Used (Cases)</td>
<td>1,873</td>
<td>65</td>
</tr>
</tbody>
</table>

Figure 3
In this comprehensive meta-analysis of 6 cohort, 6 case-control studies, and 5 RCTs, we analyzed the effect of statin use on the risk of cataracts in more than 313,200 patients. Analysis of the cohort studies showed that statin use was associated with a 13% increase in risk of cataracts. However, analysis of the case-control studies and RCTs revealed no association between statin use and the risk of cataract. The effect size of the case-control studies was marginal, namely, RR = 1.10 (95% CI, 0.99–1.23). Based on the differing characteristics of observational (case-control and cohort) studies and RCTs, such discordant results are not unexpected. Because of the rigor of RCTs, individuals at greatest risk for adverse events may be excluded. Furthermore, the subjects of RCTs may be healthier than the subjects of observational studies. The RCTs in this analysis had good internal validity, but the external validity was limited. The conclusion could not be extended to the whole population. In populations similar to the study, the conclusion was reliable. Moreover, there may be a large portion of patients similar to the patients enrolled in these RCTs. However, there are also many patients who are not similar to the patients enrolled in these RCTs. The observational studies involve more cases with different health conditions. However, in observational studies, baseline confounders can be present, which may affect the results. In such studies, relative on-on statin users, statin use may be expected to be of poorer health or to have higher risk factors that necessitate statin therapy. As a result, adverse events may be higher among statin users. Although most observational studies (including the present meta-analysis) have attempted to characterize their patients and identify validated markers of morbidity and mortality, potential unidentified confounders may exist. 35, 36 This may lead to a calculated effect size that is slightly higher than the real one. Therefore, the real effect may be of significant association. The analyses of cohort and case-control studies were limited by the considerable heterogeneity across studies. In the subgroup analysis of RCTs, the I2 values decreased significantly when subgrouped by sex, outcome assessment, age, follow-up duration, or consultation rate included/missing model (Table S5, Figures S6, S7, S9, S10, and S14). In the female (Figure S6B), no older than 60 years (Figure S9B), and less than 5 years follow-up subgroups (Figure S10B), the I2 values decreased because the weight of Cox’s study was much higher (more than 70%). In the consultation rate included...
model subgroup (Figure S14A), the I² value decreased because the weight of Lai's study was much higher (more than 80%). Consequently, the heterogeneity may be partly attributed to the outcome assessment. The evaluation criterion of various assessment methods may have varied among the studies, and patients diagnosed with cataracts by 1 method may not be diagnosed when another method is used. Further more, even when the same method of diagnosis is used, different physicians may make different decisions, especially regarding cataract surgery. In the subgroup analysis of case–control studies, the I² values were significantly decreased when sub grouped by quality assessment, study location, type of statin, CVD included/missing model, smoking included/missing model, consultation rate included/missing model, or hypertension included/missing model (Table S6, Figures S16, S17, S19, S21, S22, S23, and S25). In the quality assessment and hypertension included/missing model subgroup, the I² values of the high-quality group (Figure S16A) and the hypertension missing model (Figure S25B) decreased because the weight of the Wise-IMS study (more than 95%) and the Fong study (more than 70%) were much higher than those of the other studies. In the subgroup analyses of the study performed in Europe (Figure S17B), the CVD missing model (Figure S21B), and the consultation rate included model (Figure S23A), the I² values decreased because the included studies were derived from the same database. Therefore, the heterogeneity may be partly attributed to the types of statins. Statin have extensive pleiotropic effects that extend beyond the cholesterol-lowering properties. Different types of statin may affect cataract development by different mechanisms. Therefore, patients taking different statins may have different risks for developing cataracts. In our subgroup analysis based on the type of statin, the I² values of fluvastatin and pravastatin were significantly decreased compared with that of the overall result (Figure S19). Furthermore, the dose of statins also differed among studies. In addition to the fact that these factors may contribute to the heterogeneity, some other factors, such as ethnicity, ultraviolet exposure, and education level, may also lead to heterogeneity. The difference in the ascertainment method of statin use was also a source of heterogeneity. Klein et al.15 and Tan et al.16 determined statin use according to patient interviews, whereas in other studies, statin use was ascertained according to computerized prescription records. However, even if prescription records or interviews showed that a patient was prescribed statins, differences in patient compliance may have resulted in different degrees of exposure, which may have led to heterogeneity. Some previous studies have found that statin use has different effects on different types of cataracts.3, 5, 37 Therefore, heterogeneity may result from study variations in the types of cataract and the proportions of statin types used. Two of the included studies reported that statin use was protective against cataracts.15, 16 These 2 studies are long-term prospective cohort studies that followed patients using periodic all lens photographs. Such a design tends to achieve reliable results. However, these studies had limitations. The rate of loss to follow-up was relatively high in these 2 studies (more than 20% at the 5th year). More than the sample sizes of these 2 studies were relatively small. The analysis of the RCTs indicated that statin use does not increase the risk of cataract. Most of the individual results of included studies are consistent with this overall result. In the subgroup analyses by age and follow-up duration, no association was observed between statin use and cataract risk (Table S7). The SEA study reported that patients with aortic stenosis who were treated with simvastatin and ezetimibe had a lower risk of cataract than did patients treated with placebo.27 Because the treatment group received ezetimibe, which is a cholesterol-lowering agent, this result may be overlooked in this study.41 Heterogeneity may have also arisen from this study. The strength of our meta-analysis is the inclusion of both observational studies and RCTs and the large sample size. Despite its strengths, there are several limitations of our analysis. First, evidence of among-study heterogeneity of the observational studies was apparent. Although we performed subgroup analyses in an attempt to identify the sources of heterogeneity, these varia
blescouldnotfullyexplaintheobservedheterogeneity,suggestingthatotherunknown,confounding
variablesmightberesponsible.Second,thecofoundingfactorsvariedamongtheincludedstudies.
Becauseofthelimitationsofobservationalstudies
andRCTs,large,multicenter,pragmatic,prospectiveobservationalstudiesorregistriesshouldbe
formedinthefuturetoassesstheriskofcataracts.

The primaryendpointsshouldincludenotonlycardiovasculardiseasesbutalso
totalcomorbidity.Moreover,patientsshouldbe
stratifiedaccording to baseline confounders. Cataracts should be confirmed by objective
serial testing using validated tools, and per-
protocol analysis should be used to determine
the protocol effects on results. Finally,investigators should attempt to characterize and follow the outcomes
ofthosepatientswhodropoutofthetrials.

Basedonthepresentmeta-
analysistheseestudies,wecouldonly
conclude that there is no clear evidence
showingthatstatinuseincreasestheriskof
the most
likelycaseisthatthereisnoassociation.Because
oftheconsiderablebenefitsofstatins in cardiovascular
patients,thisissueshouldnotdetertheuseofstatins.

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