Journal of the American College of Cardiology Vol. 60, No. 10, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.07.007

STATE-OF-THE-ART PAPER

The Controversies of Statin Therapy

Weighing the Evidence

J. Wouter Jukema, MD, PhD,*†‡ Christopher P. Cannon, MD,§ Anton J. M. de Craen, MSc, PhD,‖¶ Rudi G. J. Westendorp, MD, PhD,‖¶# Stella Trompet, MSc, PhD,*‖¶

Leiden, Amsterdam, and Utrecht, the Netherlands; and Boston, Massachusetts

The debate whether statins, 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors, are safe to use has been raging since their introduction in 1987. Statins are generally well tolerated and are believed to have minimal adverse effects. However, individual, specific rare adverse events have been reported, such as elevations of liver enzymes, muscle aches, and very rarely, rhabdomyolysis. Discontinuation and/or reduction in the dose of the statin usually leads to resolution of these side effects. Recently, however, debate has focused on the possible negative long-term effects of statin treatment on cognitive decline, the incidence of cancer, and the development of diabetes mellitus. Recently, the U.S. Food and Drug Administration has expanded the warning for statins with a statement that statin use may lead to cognitive impairment. In this review, we discuss all levels of evidence, from case reports to large randomized controlled clinical trials, for the possible adverse effects of statins on cognitive decline, cancer, and diabetes. After careful consideration of all discussed scientific evidence, we conclude that there is no increased risk of cognitive decline or cancer with statin use. However, statin use is related to a small increased risk of type 2 diabetes mellitus. In view of the overwhelming benefit of statins in the reduction of cardiovascular events, we believe the small absolute risk for development of diabetes is outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended. We, therefore, suggest that clinical practice for statin therapy should not be changed on the basis of the most recent Food and Drug Administration informational warnings. (J Am Coll Cardiol 2012;60:875–81) © 2012 by the American College of Cardiology Foundation

Cardiovascular disease is the leading cause of death in industrialized countries (1). The prevention of cardiovascular disease is critically dependent on lipid-lowering therapy, most often achieved with 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Statins are the most widely prescribed class of drugs worldwide, and therapy leads to a reduction of cardiovascular events by 25% to 45%. Statins are well tolerated and are believed to have minimal adverse effects. Most common adverse effects are myopathies, elevations of liver enzymes, and very rarely, rhabdomyolysis. Discontinuation or reduction in the dose of statin treatment usually leads to resolution of these side effects. For many years, there has been debate as to whether statins are indeed as safe as reported in clinical trials (2). Most recently, the debate has centered on whether use of statins causes cognitive decline, cancer, and/or diabetes mellitus.

Recently, the U.S. Food and Drug Administration (FDA) has expanded the warning section of the label for all statins. The FDA concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective for detecting or preventing serious liver injury. Therefore, labels were revised to remove the need for routine periodic monitoring of liver enzymes.

However, the FDA also stated that statin use may increase cognitive decline (3): "FDA has been investigating reports of cognitive impairment from statin use for several years. The agency has reviewed databases that record reports of bad reactions to drugs and statin clinical trials that included assessments of cognitive function. The reports about memory loss, forgetfulness, and confusion span all statin

From the *Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; †Durrer Center for Cardiogenetic Research, Amsterdam, the Netherlands; ‡Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands; §TIMI Study Group Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; ‖Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands; ¶The Netherlands Consortium for Healthy Ageing, Leiden, the Netherlands; and the #Leyden Academy for Vitality and Ageing, Leiden, the Netherlands. Dr. Jukema has received research grant support from and was a speaker at CME accredited meetings sponsored by Astellas, AstraZeneca, Bayer, Biotronik, Boston Scientific, Daiichi Sankyo, Eli Lilly and Co., Genzyme, Medtronic, Merck-Schering-Plough, Pfizer, Orbus Neich, Novartis, Roche, Servier, Sanofi Aventis, The Netherlands Heart Foundation, the Interuniversity Cardiology of the Netherlands, and the European Community Framework KP7 Programme. Dr. Cannon is a member of the advisory boards of and has received grant support from Ainylam, Bristol-Myers Squibb, and Pfizer; has received grant support from Accumetrics, AstraZeneca, Essentialis, GlaxoSmithKline, Merck, Regeneron, Sanofi, and Takeda; and is a clinical advisor to Automated Medical Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript Received May 8 2012; revised manuscript received June 4 2012, accepted July 2, 2012.

Abbreviations and Acronyms

CHD = coronary heart disease

CI = confidence interval

FDA = Food and Drug Administration

HRT = hormone replacement therapy

OR = odds ratio

products and all age groups. Dr. Egan, Deputy Director for Safety in FDA's Division of Metabolism and Endocrinology Products, says these experiences are rare but that those affected often report feeling 'fuzzy' or unfocused in their thinking. In general, the symptoms were not serious and were reversible within a few weeks after the patient stopped using the statin. Some people affected in this way had been taking the medicine for a day; others had been taking it for years."

One might ask whether the warning of the FDA is appropriate, and we wondered where the concern about the safety of statins originates from. In this review paper, the potential influence of statins on possible adverse effects is discussed, with the focus on cognitive function, cancer, and diabetes mellitus type 2, and is set into a broader perspective based on the clinical and epidemiological evidence. We therefore discuss the 3 possible adverse events—cognitive function, cancer, and type 2 diabetes mellitus—according to 3 levels of evidence put forth to support the claims, namely, case reports, observational studies, and randomized controlled trials/systematic reviews of trials.

Case Reports

Cognition. The associations between statins and possible adverse effects have been studied since the introduction of statins in 1987 (4). Several case reports and case series have suggested a potential negative association between statins and cognitive function (5). Symptoms reported by patients in these reports include short-term and long-term memory loss, behavioral changes, impaired concentration and attention, paranoia, and anxiety. Because cholesterol synthesis is essential for neurons to function normally, it is theoretically possible that excessive inhibition of cholesterol synthetic pathways may result in neurocognitive adverse effects.

In 2003, the FDA released information on 60 case reports of memory loss associated with statins (5). The main symptom related to statins in these reports was short-term memory loss that occurred a few months after the start of statin therapy or after a dosage increase. In half the case reports, discontinuation of statin treatment resolved the symptoms, suggesting a possible causal relationship. However, because many of these case reports were from consumers and important data on medical history or other concomitant diseases or medication were missing, these findings should be interpreted with great caution, and as such, this information does not permit any firm conclusions regarding causality (5). In general, the patient population receiving statin therapy is already at risk for memory loss because of cardiac risk factors, advancing age, and amyloidosis, which could lead to detection bias. Also, the absence of objective memory tests and lipid data makes it difficult to causally link the memory change to the lipid-lowering by statins.

Cancer and diabetes mellitus type 2. No formal case reports of patients reporting incident cancer or incident diabetes coinciding with statin therapy were found in our review. Cancer and diabetes are both frequently occurring long-term clinical outcomes and might therefore not be linked to statin therapy in an individual patient.

Case reports are a valuable tool for signaling possible adverse drug effects (6). However, a case report is hardly ever definitive, and can rarely prove causation, although a case report can suggest new hypotheses and stimulate further study (7). Therefore, data from comparative studies are necessary, either from observational studies or randomized trials.

Observational Research

Cognition. Many observational studies have investigated the association between statin use and cognitive function (4). We identified 9 observational studies that studied this relationship (8–16). Four studies showed beneficial effects of statins on cognitive performance (8–11), 3 studies found no effect on cognitive function (12,15,16), and 2 studies found an increased risk of cognitive impairment associated with statin use (13,14). Given the heterogeneity of the outcomes, the results of the observational studies are inconclusive. One of the main problems with investigating the association between statin therapy and possible adverse effects in observational studies is confounding by indication. First, the patient population receiving statin therapy in observational studies is already at risk for vascular disease, has multiple cardiac risk factors, and is on average older than those not receiving statin therapy. Therefore, these subjects are by definition more prone to develop cognitive impairment (17). Second, in observational studies a comparison is made between prevalent users of statins and nonusers. That leads to another form of selection bias as prevalent users have survived during their treatment period. If treatment decreases the risk of a specific outcome, the group of prevalent users will be enriched with susceptible patients compared with the nonusers. Conversely, more resilient patients will be in the user group if treatment increases the risk of outcome (17). Statistical correction for imbalances between treatment groups in observational studies has proven to be unreliable (18). An evident example of such discrepancy is found in studies performed to analyze the effect of postmenopausal hormone replacement therapy (HRT) on coronary heart disease (CHD). Most observational studies found a lower risk of CHD in users of HRT compared with nonusers, a finding that was interpreted as a protective effect of HRT on CHD risk. However, a large randomized clinical trial found a higher CHD risk among incident users of HRT compared with placebo users (19).

Cancer. Numerous observational studies have reported an association between low plasma cholesterol levels and higher

risk of cancer (20–25). That has led to concerns that treatment with statins, which lower cholesterol levels, might increase cancer risk. However, these observed associations between low plasma cholesterol and increased risk of cancer might originate from reverse causality or confounding. For example, low plasma cholesterol levels might be caused by a hypocholesterolemic effect of cancer in pre-clinical stages (26). In that case, subjects with cancer would have an abnormally low cholesterol level because of the cancer, not vice versa (reverse causality). Furthermore, confounding factors such as age, smoking, and alcohol use might also explain some of the observed associations. Moreover, subjects with low cholesterol may simply live long enough to develop cancer.

To try to overcome the problems of reverse causality and confounding, a Mendelian randomization study was performed. Mendelian randomization is based on Mendel's law that inheritance of 1 genetic trait is independent of inheritance of other traits. We used the *APOE* genotype to assess the association between cholesterol levels and cancer (27). We found that subjects, when grouped by their baseline cholesterol levels, indeed had a higher cancer risk when their baseline cholesterol levels were lower. However, when subjects were categorized according to their *ApoE* genotypes, which also resulted in groups with significantly different cholesterol levels, no increased risk of cancer was observed in the group with low cholesterol levels (27). These findings suggest that low levels of cholesterol are not causally related to an increased risk of cancer—again showing that results of observational studies are difficult to interpret with regard to causality.

Type 2 diabetes mellitus. The relation between statin treatment and incident diabetes has not been described in many observational studies. In a large observational study of 345,417 subjects, Sukhija et al. (28) found statin use to be associated with higher fasting glucose levels. More recently, the Women's Health Initiative investigated this relation in 161,808 postmenopausal women ages 50 to 79 years (29). Statin use at baseline was associated with a 1.7 higher risk of type 2 diabetes mellitus. This association remained after adjusting for potential confounders, and was observed for all types of statins. However, this study had methodologic limitations because the investigators could not adjust for baseline cholesterol levels, which had been measured in only 10% of the participants. In addition, they did not analyze new users of statins and their risk, and the accuracy of the diagnosis of incident diabetes was not optimal.

Limitations of observational studies. Randomized clinical trials are usually the preferred strategy for obtaining evidence on the effects of clinical interventions. Randomization prevents selection bias, which results in a similar baseline prognosis for occurrence of the clinical outcome in the treatment group and the placebo group. In observational studies, users have a different prognosis for the clinical outcome compared to nonusers, as allocation of treatment by clinicians is usually based on specific prognostic factors. Even rigorous adjustment for known prognostic factors does not result in unbiased estimates of treatment effects. On the contrary, the evidence on the safety of a clinical intervention (unintended effects) might be assessed by both observational studies and randomized trials. The drawback of assessing the unintended effects in randomized trials is that they are frequently under-powered to find associations with adverse outcomes and that their follow-up is often relatively short. Assessing whether the unintended effects of a clinical intervention can be validly done from observational studies, being either case-control studies or prospective follow-up studies, depends on the judgment whether treated and untreated groups have a similar baseline prognosis for development of the adverse effect. Because treatment groups will frequently have similar baseline prognosis for the adverse effect under study, observational research may yield valid estimates (30,31). That is why observational studies often yield results similar to those of randomized controlled trials for unintended effect of clinical interventions (32,33).

To investigate the relation between statins and adverse events like cognition, cancer, and diabetes, the use of observational studies may not be adequate because the prognostic factors for the intended effects of statin treatment (reduction of cardiovascular disease) are the same risk factors for cognitive function (34,35), cancer (36,37), and diabetes (38,39). Because the incidences of cognitive decline, cancer, and diabetes are relatively high among patients for whom statin treatment is indicated, and follow-up of patients in these trials is generally long enough for the possible adverse effects to occur (often 5 years), randomized trials are the most appropriate design to assess whether statin treatment is associated with an increase of these events.

Randomized Controlled Trials and Systematic Reviews

Cognition. Two large randomized controlled clinical trials have examined the effect of statins on cognitive function as the major secondary endpoint of the studies (40,41). First, the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk for Vascular Disease) investigated, in 5,804 participants, the effect of pravastatin (40 mg daily) on cognitive function, measured with an extensive set of validated tests for cognitive function (40). Every 9 months, cognitive function was assessed, with a mean follow-up period of 42 months. As expected over time, on average, a general significant cognitive decline was indeed observed in all subjects, indicating that the measurements were appropriate. However, and most importantly, the decrease in cognitive function over time was no different between pravastatin treatment versus placebo (Fig. 1) (42). Also, no adverse events such as memory loss or confusion were reported to be more common with pravastatin use compared to placebo.

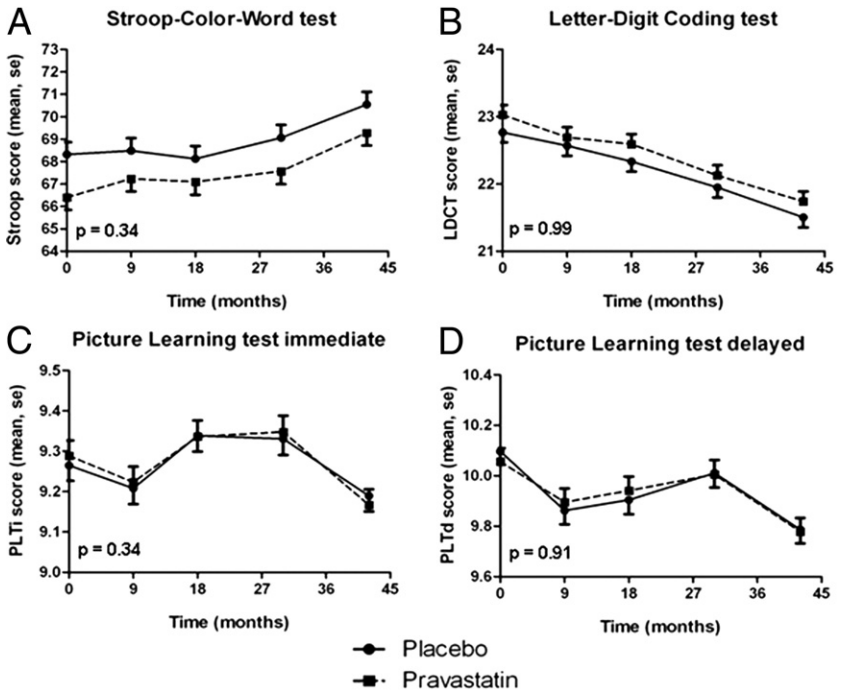

Figure 1 **Effect of Pravastatin on Cognitive Function Among Participants of the PROSPER Study**

The p values represent the statistical significance of the difference in test score changes over time between statin users **(squares)** and nonusers **(circles)** in the PROSPER study. Means were assessed using linear mixed models adjusted for sex, age, educational status, country, and version of test where appropriate. **(A)** Stroop-color-word test; **(B)** letter-digit coding test (LDCT); **(C)** picture learning test immediate (PLTi); **(D)** picture learning test delayed (PLTd). Figure was originally published in Trompet et al. (42); permission for its use granted by the publisher.

The other randomized clinical trial, the Heart Protection Study, investigated the effect of simvastatin (40 mg daily) on cognitive function in 20,536 participants (41). Cognitive function was assessed using the Telephone Interview for Cognitive Status questionnaire. After a mean follow-up period of 5.3 years, no significant change in cognitive function was shown between simvastatin- and placebo-treated patients (43). Because cognitive function after statin/placebo therapy was measured only once at the end of the study, the drop-out due to cognitive impairment during the study could have biased the results. The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study reported no difference in cognitive function between rosuvastatin and placebo users at the end of the trial; only a slight increase in subjects reporting confusional state in the rosuvastatin group was found (44). However, the JUPITER trial was not designed to measure neurocognitive status in a systematic way, so no definite conclusions can be drawn (44).

Twelve other small randomized controlled trials have studied the relationship between statin use and cognitive function as a primary outcome (45–56). The majority of the trials, 9 studies, found no change in cognitive function between statin and placebo users (45–49,51–53,55). One trial found a detrimental effect of statin use on cognitive function measured with the 4-word memory test (50). Two studies found a benefit in cognitive function (54,56).

Taking all this evidence together from the randomized controlled clinical trials, we believe that there is no evidence to conclude that statins have detrimental (or beneficial) effects on cognitive function. That does not exclude the possibility that for an individual patient a rare side effect may occur, as is the case for any other type of medication.

Cancer. As stated earlier, the discussion whether statins might cause an increased risk of cancer has been ongoing since the finding that low levels of low-density lipoprotein cholesterol are associated with a higher risk of cancer incidence. That raised the question whether lowering low-density lipoprotein cholesterol levels with statin treatment would increase risk of cancer. Cancer incidence has been assessed in all large randomized controlled trials (57). Until now, only 2 randomized controlled trials have reported an increased risk of cancer in the statin group compared to the placebo group. The PROSPER study found a 1.25 increased risk for cancer incidence for the statin-treated patients compared to the placebo group (40). Also, in the LIPID (Long-Term Intervention With Pravastatin in Ischemic Disease) trial, an increased cancer risk in the pravastatin group compared to placebo users was found when they analyzed this in an elderly subgroup (58). Bonovos et al.

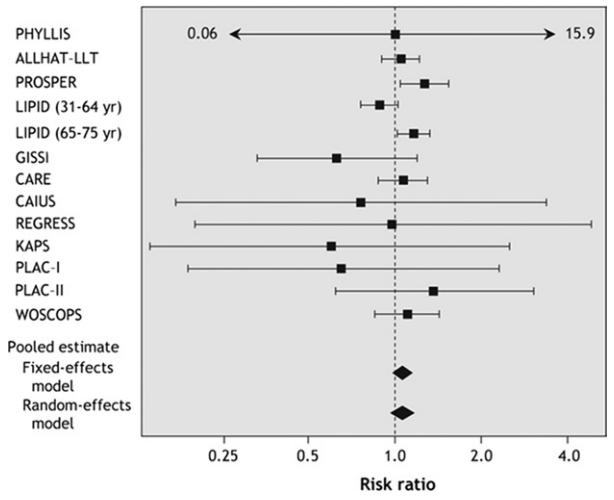

Figure 2 **Meta-Analysis of Pravastatin Therapy and Cancer Risk**

The risk ratios and 95% confidence intervals are displayed on a logarithmic scale. Figure was originally published in Bonovas and Sitaras (60); permission for its use granted by the publisher. © Canadian Medical Association. This work is protected by copyright and the making of this copy was with the permission of Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law.

(59,60) performed a systematic review to investigate the effect of statin on cancer incidence. They pooled data from 12 large randomized controlled trials and found a nonsignificant overall estimate of 1.07 (95% confidence interval [CI]: 0.97 to 1.18) with the random-effects model (Fig. 2). They also performed meta-regression to investigate the impact of age on this association (60), and found that the risk ratios of cancer associated with pravastatin therapy increased with advancing age. The authors of the PROSPER study reported their finding as a possible chance finding due to a skewed distribution of subjects with latent cancer (40). Now they have extended their follow-up period by 10 years (from 3.5 to 14 years of follow-up) and found no increased risk of cancer incidence for subjects treated with statins compared to placebo (Prof. Ian Ford, personal communication, January 30, 2012).

Numerous other recent systematic reviews have also shown no increased risk for cancer incidence with statin treatment (2,33,57,61–65). The most recent meta-analysis included 33 randomized controlled trials with data on first incident cancers recorded after randomization (2). The incidence of cancer was not different between statin groups and control groups (3,706 [5.9%] vs. 3,746 [6.0%]; odds ratio [OR]: 0.99, 95% CI: 0.94 to 1.04, p = 0.69). In conclusion, from all these systematic reviews and large meta-analyses, we conclude that there is no increased risk of incident cancer with statin treatment.

Type 2 diabetes mellitus. Researchers of large randomized controlled trials have reported conflicting results about the development of type 2 diabetes mellitus after receiving statin therapy (66). For example, the JUPITER trial reported an increased incidence of diabetes in the rosuvastatin group compared to the placebo group (67), whereas the WOSCOPS (West of Scotland Coronary Prevention Study) trial had reported that pravastatin appeared to reduce the risk of diabetes (68). A large meta-analysis was performed to

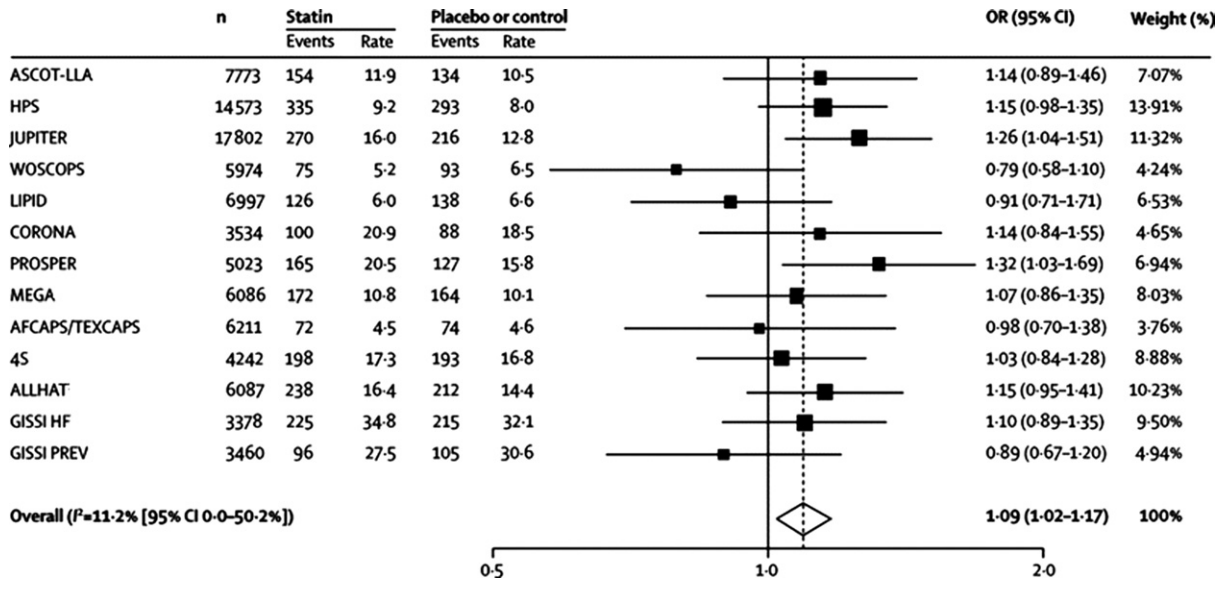

Figure 3 **Association Between Statin Therapy and Incident Diabetes in 13 Major Cardiovascular Trials**

Events per 1,000 patient-years. Weights are from random-effects analysis. Figure was originally published in Sattar et al. (66); permission for its use granted by the publisher. CI = confidence interval; OR = odds ratio.

investigate the effect of statins on the risk of diabetes systematically (66). Thirteen statin trials involving a total of 91,140 participants were identified that investigated this association. Statin therapy was associated with a 9% increased risk for incident diabetes (OR: 1.09; 95% CI: 1.02 to 1.17), as shown in Figure 3. There was, however, of course a benefit in a reduction in CHD death, myocardial infarction, and stroke. Meta-regression showed a stronger association in trials with older participants. As such, there was no apparent increased risk in trials in which patients were on average age 60 years or younger (64). Conversely, the risk was present in the older population, a group for which the absolute benefit of statin therapy would also be greater (66). Therefore, benefit was seen to outweigh risk, especially for younger patients, for whom no increased risk was apparent in this study.

Another recent meta-analysis showed that use of intensive-dose statin therapy compared with moderate-dose statin therapy led to a higher incidence of new-onset diabetes (OR: 1.12, 95% CI: 1.04 to 1.22) (69). To put this into a clinical perspective, intensive-dose statin therapy also led to fewer major cardiovascular events compared to moderate-dose statin therapy (OR: 0.84, 95% CI: 0.75 to 0.94) (69). Therefore, the large benefit of statins for cardiovascular events outweighs the small absolute risk for development of diabetes.

A potential mechanism to explain the findings of the higher incidence with statin therapy has not yet been identified. One possibility might be that statins directly affect muscle or insulin action, resulting in higher diabetes incidence. Animal models have shown that statin-induced myopathy is associated with the development of muscle insulin resistance (70). However, more research is needed to provide more information regarding the underlying mechanism of the small statin-related diabetes risk.

Conclusions

Recent large meta-analyses and systematic reviews have shown no convincing evidence for change in cognitive function or risk of cancer after statin use. However, a small increased risk for incident type 2 diabetes mellitus has been observed. In view of the overwhelming benefit of statins for reduction of cardiovascular events by 25% to 45%, the small increase in relative risk for the development of diabetes is outweighed by the cardiovascular benefit in the short and medium term for patients for whom statin therapy is recommended. We, therefore, suggest that clinical practice for statin therapy should not be changed for patients with high cardiovascular risk or existing cardiovascular disease. However, the newly identified diabetes risk should be taken into account if statin therapy is considered for patients at low cardiovascular risk or for patient groups for which cardiovascular benefit has not been proven.

Reprint requests and correspondence: Prof. J. Wouter Jukema, Department of Cardiology, Leiden University Medical Center, P.O. Box 9600, Leiden 2300 RC, the Netherlands. E-mail: j.w.jukema@lumc.nl.

REFERENCES

1. McGovern PG, Pankow JS, Shahar E, et al. Recent trends in acute coronary heart disease—mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. N Engl J Med 1996;334:884–90.
2. Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. Q J Med 2012;105:145–57.
3. FDA.org—The Center For Health and Wellness. Available at: http://www.fda.org/drugs/drugssafety/ucm293101.htm. Accessed April 25, 2012.
4. Rojas-Fernandez CH, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother 2012;46:549–57.
5. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871–80.
6. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008;5:e67.
7. Morris BA. The importance of case reports. Can Med Assoc J 1989;141:875–6.
8. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet 2000;356:1627–31.
9. Hajjar I, Schumpert J, Hirth V, Wieland D, Eleazer GP. The impact of the use of statins on the prevalence of dementia and the progression of cognitive impairment. J Gerontol 2002;57A:M414–8.
10. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002;59:223–7.
11. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol 2002;59:378–84.
12. Starr JM, McGurn B, Whiteman M, Pattie A, Whalley LJ, Deary IJ. Life long changes in cognitive ability are associated with prescribed medications in old age. Int J Geriatr Psychiatry 2004;19:327–32.
13. Agostini JV, Tinetti ME, Han L, McAvay G, Foody JM, Concato J. Effects of statin use on muscle strength, cognition, and depressive symptoms in older adults. J Am Geriatr Soc 2007;55:420–5.
14. Redelmeier DA, Thiruchelvam D, Daneman N. Delirium after elective surgery among elderly patients taking statins. Can Med Assoc J 2008;179:645–52.
15. Glasser SP, Wadley V, Judd S, et al. The association of statin use and statin type and cognitive performance: analysis of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Clin Cardiol 2010;33:280–8.
16. Benito-Leon J, Louis ED, Vega S, Bermejo-Pareja F. Statins and cognitive functioning in the elderly: a population-based study. J Alzheimers Dis 2010;21:95–102.
17. Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. Am J Epidemiol 2012;175:250–62.
18. Vandenbroucke JP. The HRT controversy: observational studies and RCTs fall in line. Lancet 2009;373:1233–5.
19. Magliano DJ, Rogers SL, Abramson MJ, Tonkin AM. Hormone therapy and cardiovascular disease: a systematic review and meta-analysis. BJOG 2006;113:5–14.
20. Cowan LD, O'Connell DL, Criqui MH, Barrett-Connor E, Bush TL, Wallace RB. Cancer mortality and lipid and lipoprotein levels. Lipid Research Clinics Program mortality follow-up study. Am J Epidemiol 1990;131:468–82.
21. Iribarren C, Reed DM, Chen R, Yano K, Dwyer JH. Low serum cholesterol and mortality. Which is the cause and which is the effect? Circulation 1995;92:2396–403.
22. Keys A, Aravanis C, Blackburn H, et al. Serum cholesterol and cancer mortality in the Seven Countries Study. Am J Epidemiol 1985;121:870–83.

23. Knekt P, Reunanen A, Aromaa A, Heliovaara M, Hakulinen T, Hakama M. Serum cholesterol and risk of cancer in a cohort of 39,000 men and women. J Clin Epidemiol 1988;41:519–30.
24. Schuit AJ, Van Dijk CE, Dekker JM, Schouten EG, Kok FJ. Inverse association between serum total cholesterol and cancer mortality in Dutch civil servants. Am J Epidemiol 1993;137:966–76.
25. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet 1997;350:1119–23.
26. Kritchevsky SB, Kritchevsky D. Serum cholesterol and cancer risk: an epidemiologic perspective. Annu Rev Nutr 1992;12:391–416.
27. Trompet S, Jukema JW, Katan MB, et al. Apolipoprotein E genotype, plasma cholesterol, and cancer: a Mendelian randomization study. Am J Epidemiol 2009;170:1415–21.
28. Sukhija R, Prayaga S, Marashdeh M, et al. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Invest Med 2009;57:495–9.
29. Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med 2012;172:144–52.
30. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92.
31. Concato J, Horwitz RI. Beyond randomised versus observational studies. Lancet 2004;363:1660–1.
32. Miettinen OS. The need for randomization in the study of intended effects. Stat Med 1983;2:267–71.
33. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363:1728–31.
34. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277–81.
35. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322:1447–51.
36. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54:8–29.
37. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
38. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790–7.
39. Seidell JC. Obesity, insulin resistance and diabetes—a worldwide epidemic. Br J Nutr 2000;83 Suppl 1:5–8.
40. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30.
41. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757–67.
42. Trompet S, van VP, de Craen AJ, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol 2010;257:85–90.
43. Clarke R, Xu P, Bennett D, et al. Lymphotoxin-alpha gene and risk of myocardial infarction in 6,928 cases and 2,712 controls in the ISIS case-control study. PLoS Genet 2006;2:e107.
44. Endocrinologic and Metabolic Drugs Advisory Committee Meeting, Gaithersburg, Maryland, December 15, 2009. CRESTOR (Rosuvastatin calcium), NDA 21-366, JUPITER, Mary Dunne Roberts, MD, Division of Metabolism and Endocrinology Products. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm194918.pdf. Accessed May 30, 2012.
45. Harrison RW, Ashton CH. Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers. Br J Clin Pharmacol 1994;37:231–6.
46. Kostis JB, Rosen RC, Wilson AC. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. J Clin Pharmacol 1994;34:989–96.
47. Cutler N, Sramek J, Veroff A, Block G, Stauffer L, Lines C. Effects of treatment with simvastatin and pravastatin on cognitive function in patients with hypercholesterolaemia. Br J Clin Pharmacol 1995;39:333–6.
48. Gengo F, Cwudzinski D, Kinkel P, Block G, Stauffer L, Lines C. Effects of treatment with lovastatin and pravastatin on daytime cognitive performance. Clin Cardiol 1995;18:209–14.
49. Santanello NC, Barber BL, Applegate WB, et al. Effect of pharmacologic lipid lowering on health-related quality of life in older persons: results from the Cholesterol Reduction in Seniors Program (CRISP) pilot study. J Am Geriatr Soc 1997;45:8–14.
50. Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med 2004;117:823–9.
51. Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. Am J Med 2000;108:538–46.
52. Gibellato MG, Moore JL, Selby K, Bower EA. Effects of lovastatin and pravastatin on cognitive function in military aircrew. Aviat Space Environ Med 2001;72:805–12.
53. Golomb BA, Dimsdale JE, White HL, Criqui MH. Do low dose statins affect cognition? Results of the UCSD statin study. Circulation 2006;114:II289.
54. Parale GP, Baheti NN, Kulkarni PM, Panchal NV. Effects of atorvastatin on higher functions. Eur J Clin Pharmacol 2006;62:259–65.
55. Summers MJ, Oliver KR, Coombes JS, Fassett RG. Effect of atorvastatin on cognitive function in patients from the Lipid Lowering and Onset of Renal Disease (LORD) trial. Pharmacotherapy 2007;27:183–90.
56. Berk-Planken I, de Konig I, Stolk R, Jansen H, Hoogerbrugge N. Atorvastatin, diabetic dyslipidemia, and cognitive functioning. Diabetes Care 2002;25:1250–1.
57. Alsheikh-Ali AA, Trikalinos TA, Kent DM, Karas RH. Statins, low-density lipoprotein cholesterol, and risk of cancer. J Am Coll Cardiol 2008;52:1148–49.
58. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. Ann Intern Med 2001;134:931–40.
59. Bonovas S, Filioussi K, Flordellis CS, Sitaras NM. Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. J Clin Oncol 2007;25:3462–8.
60. Bonovas S, Sitaras NM. Does pravastatin promote cancer in elderly patients? A meta-analysis. Can Med Assoc J 2007;176:649–54.
61. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.
62. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009;338:b2376.
63. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74–80.
64. Emberson JR, Kearney PM, Blackwell L, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;7:e29849.
65. Bonovas S, Nikolopoulos G, Sitaras NM. Efficacy and safety of more intensive lowering of LDL cholesterol. Lancet 2011;377:715–6.
66. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735–42.
67. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
68. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001;103:357–62.
69. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305:2556–64.
70. Mallinson JE, Constantin-Teodosiu D, Sidaway J, Westwood FR, Greenhaff PL. Blunted Akt/FOXO signalling and activation of genes controlling atrophy and fuel use in statin myopathy. J Physiol 2009;587:219–30.

Key Words: adverse effects ■ cancer ■ cognitive decline ■ diabetes mellitus ■ statins.