Statin Therapy: Diabetes Mellitus Risk and Cardiovascular Benefit in Primary Prevention

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ABSTRACT: **Background:** The salutary effects of statin therapy in patients with cardiovascular disease (CVD) are well established. Although generally considered safe, statin therapy has been reported to contribute to induction of diabetes mellitus (DM).

Objectives: To assess the risk-benefit of statin therapy, prescribed for the prevention of CVD, in the development of DM.

Methods: In a population-based real-life study, the incidence of DM and CVD were assessed retrospectively among 265,414 subjects aged 40–70 years, 17.9% of whom were treated with statins. Outcomes were evaluated according to retrospectively determined baseline 10 year cardiovascular (CV) mortality risks as defined by the European Systematic COronary Risk Evaluation, statin dose-intensity regimen, and level of drug adherence.

Results: From 2010 to 2014, 5157 (1.9%) new cases of CVD and 11,637 (4.4%) of DM were observed. Low-intensity statin therapy with over 50% adherence was associated with increased DM incidence in patients at low or intermediate baseline CV risk, but not in patients at high CV risk. In patients at low CV risk, no CV protective benefit was obtained. The number needed to harm (NNH; incident DM) for low-intensity dose regimens with above 50% adherence was 40. In patients at intermediate and high CV risk, the number needed to treat was 125 and 29; NNH was 50 and 200, respectively.

Conclusions: Prescribing low-dose statins for primary prevention of CVD is beneficial in patients at high risk and may be detrimental in patients at low CV risk. In patients with intermediate CV risk, our data support current recommendations of individualizing treatment decisions.

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KEY WORDS: cardiovascular disease (CVD), diabetes mellitus (DM), drug-induced adverse event, primary prevention, statin drugs

The role of statins in reducing serum low-density lipoprotein-cholesterol (LDL-C) levels and risk ratio for cardiovascular disease (CVD) as well as primary prevention is well established [1-3].

Statin therapy is generally considered safe, with a low rate of reversible side effects. Recently, statin therapy has been found to be associated with an excess risk of incident diabetes mellitus (DM) [4,5]. This hyperglycemic effect might induce diabetic complications and offset its cardiovascular protective effect. While for secondary prevention the consensus is that the benefits of statins outweigh its risks [6,7], the risk-benefit balance of statins in primary prevention is less clear.

The objective of the present study was to examine the risk of developing DM versus the benefit of preventing CVD among healthy individuals treated with statins for primary prevention compared to non-treated subjects in a large Israeli cohort.

PATIENTS AND METHODS

This retrospective cohort study was conducted by the Maccabi Healthcare Services (MHS), a health maintenance organization in Israel that serves 2.1 million members. All data were obtained from MHS automated databases and were used to gather information on all prescriptions dispensed in the community as well as and biochemistry results. The study was approved by the MHS institutional review board. The cohort included MHS members aged 40 to 70 years old in 2010 who were enrolled in MHS in 2008 with no record of DM or CVD, who did not have a statin prescription for at least 2 years before the index date (the date of the first statin purchase), and who from 1 January 2010 to 31 December 2014 had at least one prescription filled. From the total number who met the criteria, we identified 265,414 eligible individuals. Incident cases of DM or CVD were determined using DM and CVD registries that are routinely updated using the search engines of the MHS central electronic medical record files. These files include personal data, hospitalization records, history of medical procedures, laboratory test findings, medications prescribed, imaging results, and personal physician diagnoses. The CVD registry is comprised of patients diagnosed with CVD including ischemic heart disease, congestive heart failure, and peripheral vascular disease. The maximum follow-up was 5 years. The European Systematic COronary Risk Evaluation (SCORE) formula was used to stratify the cohort into three 10 year risk levels: low risk

(≤ 1%), intermediate risk (> 1 to < 5%), and high risk (≥ 5%). The SCORE is used for primary prevention purposes and uses 10 year cardiovascular mortality risk levels. We calibrated the formula to fit the MHS population (unpublished data) and validated its 10 year accuracy prior to the current study (receiver operating characteristic [ROC] 0.76, asymptotic 95% confidence interval [95%CI] 0.75–0.77) The chi-square test for calibration failed to refute the null hypothesis of fit. In accordance with the American College of Cardiology/American Heart Association (ACC/AHA) 2013 guideline classification of statin therapy [8], initial statin therapy was divided into three relative efficacy levels: low intensity regimen (< 30% expected LDL-C reduction), moderate intensity regimen (31–50% expected LDL-C reduction), and high intensity regimen (> 51% expected LDL-C reduction). In accordance with previous studies [9], adherence was calculated using the mean proportion of days covered (PDC) by dividing the quantity of statins dispensed by the total interval from index date to outcome diagnosis, death of the patient, or the end of the study period (31 December 2014), whichever occurred first. We referred to two levels of PDC: less than 50% (low) and 50% or more (high) adherence, respectively. The chi-square test for categorical variables and one-way analysis of variance test for continuous variables were performed to determine significant differences in baseline characteristics and cardiovascular risk levels and between levels of intensity of statin therapy and outcomes. Cox proportional hazard regression with years of follow-up as the time scale was used to estimate hazard ratios (HR) and 95%CI and to identify variables significantly associated with increased risk of outcome. Analyses were conducted separately for DM and CVD outcomes. The full multivariate model included the following baseline values: age (in 1 year increments), gender, total cholesterol, cardiovascular SCORE risk, PDC, and intensity level of the initial statin therapy. Analyses were stratified by baseline body mass index (BMI) levels. We used adjusted Kaplan–Meier curves to compare the time to new onset of DM and CVD in each cardiovascular risk group. We calculated the number needed to treat (NNT) or number needed to harm (NNH) using absolute risk estimates at 5 years of follow-up [10]. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

The study was comprised of 265,414 subjects, 43% male, mean age 50.8 years. Average BMI was 27.4 kg/m^2 and total cholesterol 5.19 mmol/L. A total of 19% had hypertension; 63% of the total number of participants were at low risk for cardiovascular mortality (≤ 1% in 10 years), 33.6% at moderate risk, and 3.4% at high risk (≥ 5%) [Table 1].

Some 47,611 (17.9%) patients purchased statins during the study period, of which 43,229 (90.8%) were of low intensity regimen. Simvastatin was the most frequently prescribed statin, purchased by 32,389 (68%) patients. Although a formal evaluation of the overall cardiovascular risk was not performed prior to the decision to prescribe chronic statin therapy, the actual percentage of subjects treated with statins increased as the calculated risk SCORE increased: 3.3%, 7%, and 11.1% for < 1% risk, 1–5% risk and ≥ 5% risk, respectively, in the low statin with low adherence group; and 8.2%, 17.2%, and 25.2% for < 1% risk, 1–5% risk, and ≥ 5% risk, respectively, in the low statin with high adherence group.

The distribution of demographics and risk factors according to statin treatment is shown in Table 1A. Subjects who received statins were older, were more frequently male, had a higher BMI, and presented more frequently with hypertension and hypercholesterolemia, compared to subjects who received no statins. The level of adherence did not correlate with demographics and risk factors.

Over the 5 year evaluation period, 11,637 subjects (4.4 %) were diagnosed with DM and 5157 (1.9%) with CVD. The relative risk (RR) for DM and CVD was 3.8 and 9, respectively,

Table 1. Distribution of demographics and risk factors **[A]** According to cardiovascular SCORE risk **[B]** According to statin treatment

A

SCORE 10 year CV mortality Risk	N (%)	Male gender	Age, mean ± SD	BMI, mean ± SD	Hypertension N (%)	Total cholesterol (mmol/L), mean ± SD	LDL (mmol/L), mean ± SD
≤ 1%	167,207 (63.0)	34.4%	46.4 ± 4.4	26.8 ± 5.1	17,416 (10.4)	5.05 ± 0.84	3.09 ± 0.71
1–5%	89,067 (33.6)	55.2%	57.7 ± 5.4	27.8 ± 4.8	28,333 (31.8)	5.38 ± 0.85	3.35 ± 0.71
≥ 5%	9140 (3.4)	65.9%	64.6 ± 4.0	28.1 ± 4.7	5042 (55.2)	5.59 ± 0.93	3.52 ± 0.77
All	265,414 (100)	42.5%	50.8 ± 7.6	27.2 ± 5.0	50,791 (19.1)	5.19 ± 0.87	3.2 ± 0.73
P value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

B

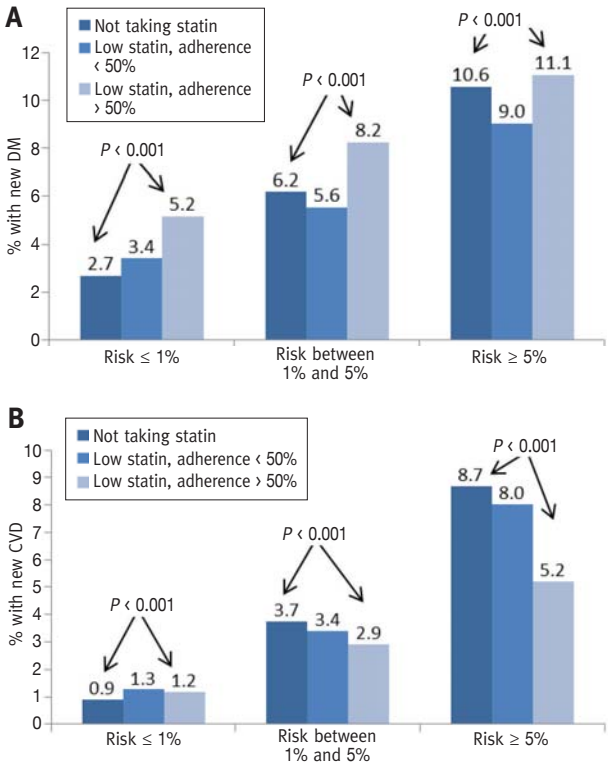
Statin use	N (%)	Male gender	Age, mean ± SD	BMI, mean ± SD	Hypertension, N (%)	Total cholesterol (mmol/L) mean ± SD	LDL (mmol/L) mean ± SD
No statin	217,803 (83.4)	41.4%	50.2 ± 7.4	27.2 ± 5.2	36,802 (16.9)	5.05 ± 0.8	3.08 ± 0.68
Low statin, adherence < 50%	25,986 (10.0)	45.2%	53.0 ± 7.4	28.3 ± 5.0	7078 (27.2)	5.84 ± 0.85	3.77 ± 0.70
Low statin, adherence > 50%	17,233 (6.6)	47.4%	54.3 ± 7.5	28.0 ± 4.8	5551 (32.2)	5.76 ± 0.78	3.69 ± 0.66
All	261,022 (100)	42.2%	50.8 ± 7.6	27.4 ± 5.2	49,431 (18.9)	5.17 ± 0.86	3.19 ± 0.72
P value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

BMI = body mass index, CV = cardiovascular, LDL = low-density lipoprotein, SCORE = European Systematic COronary Risk Evaluation

for subjects in the highest risk compared with the lowest risk cardiovascular SCORE risk group.

The percentage of subjects who were treated with low dose statin and developed DM during the study stratified by cardiovascular SCORE risk levels and by statin intensity regimen are shown in Figure 1A. In the low SCORE risk category, the incidence of DM in subjects with low statin and high adherence was twice that of subjects not receiving statins, (5.2% vs. 2.7%; RR 1.9, $P < 0.001$). This risk ratio was smaller for subjects at moderate cardiovascular SCORE risk, (8.2% vs. 6.2%; RR 1.3, $P < 0.001$), and virtually disappeared in subjects with high cardiovascular SCORE risk.

Figure 1. Risk of developing **[A]** diabetes mellitus (DM) or **[B]** cardiovascular disease (CVD) by cardiovascular risk group, statin intensity and level of adherence



*P values refer to the comparisons of no statins vs. low statins and high adherence (indicated by arrows)

The percentage of subjects who were treated with moderate dose statin and high adherence who developed DM during the study was 4.8%, 8.1%, and 11.2% in the low, moderate, and high SCORE risk categories, respectively.

The association of statin therapy with the incidence of CVD is shown in Figure 1B. Statin therapy was associated with a reduced incidence of CVD in patients at moderate and high cardiovascular SCORE risk. This association was more pronounced in patients with high adherence. Increased statin dose in subjects with high adherence was associated with further decreasing CVD risk. Assuming causality, the NNT with low intensity regimens and high adherence for 5 years to prevent one case of CVD and the NNH to cause one case of DM, were calculated. For high and intermediate CVD risk subjects the NNT was 29 and 125, respectively, while for low CVD risk there was no cardiovascular benefit. For high, intermediate, and low CVD risk subjects the NNH was 200, 50, and 40, respectively. In subjects with low adherence the association of statin therapy was negligible with both CVD and DM.

The cardiovascular risk SCORE does not take BMI into account. Thus, we examined the relationship between obesity and the risk of developing DM [Table 2]. The lowest incidence of DM was observed among subjects who did not receive statins and had a normal BMI (≥ 18 kg/m^2 and < 26 kg/m^2) at the beginning of the study: 2.69 cases per 1000 person-years (those who had normal BMI both at the beginning and the end of the study had an even lower rate of 2.2 cases per 1000 person-years, these data are not shown in Table 2). The highest incidence was observed in those who were treated with low statins and had high adherence and were morbidly obese (BMI 35–60 kg/m^2): 43.92 cases per 1000 person-years. Statin therapy was associated with increased risk of DM at all BMI values. However, comparison of the incidence of DM in subjects not treated with statins to that of subjects treated with low intensity regimens and high adherence, shows that the excess risk of DM was highest in subjects with normal BMI throughout the 5 year study period (6.74 kg/m^2 vs. 2.69 kg/m^2 per 1000, RR 2.5) and lowest in obese individuals (43.92 kg/m^2 vs. 32.35 kg/m^2 per 1000, RR 1.4).

We used adjusted Kaplan–Meier curves to compare time to new-onset DM and CVD in low statin treatment group [Figure 2A, Figure 2B) and Cox regression analyses of variables effect size and significance on outcomes incidence.

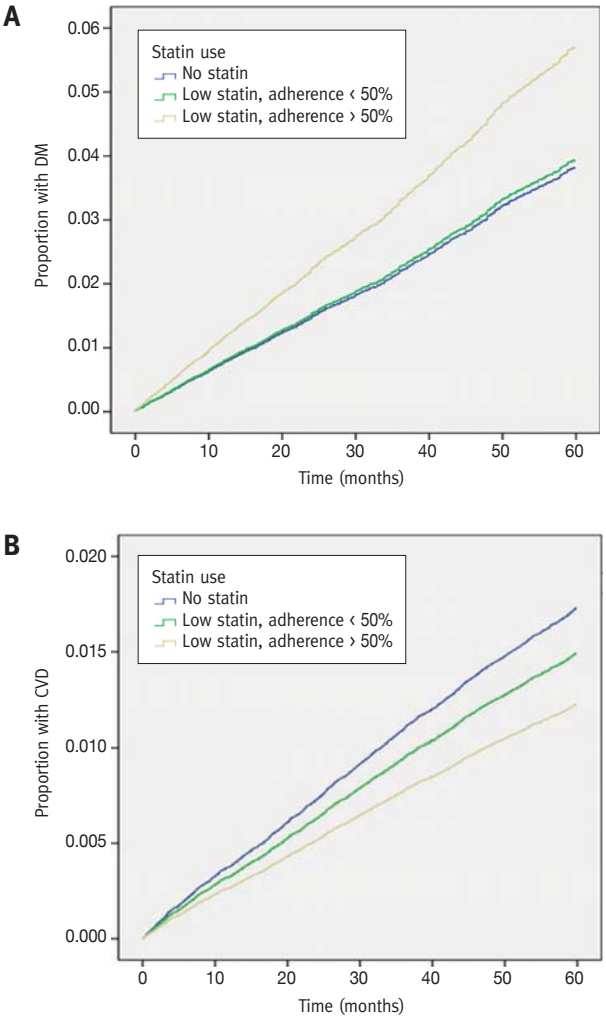
The Cox multi-regression analyses (on parameters listed in Table 1A) show that statin treatment was significantly associ-

Table 2. Incidence of diabetes mellitus in subjects treated with low dose statins and various adherence levels according to BMI

	No Statin		Low statin, adherence ‹ 50%		Low statin, adherence ≥ 50%		All	
Statin use	N with diabetes	Events for 1000 PYs	N with diabetes	Events for 1000 PYs	N with diabetes	Events for 1000 PYs	N with diabetes	Events for 1000 PYs
Missing BMI	907	4.53	50	6.01	199	9.75	1156	5.05
BMI 12–18	14	2.05	0		0		14	1.88
BMI 18–26	1106	2.69	87	4.48	336	6.74	1529	3.19
BMI 26–30	2238	9.08	173	9.66	597	14.12	3008	9.81
BMI 30–35	2473	18.14	195	17.28	631	25.05	3299	19.09
BMI 35–60	1842	32.35	107	23.97	411	43.92	2360	33.35
All (for BMI 12–60)	7673	8.95	562	10.56	1975	15.54	10,210	9.84

BMI = body mass index, PYs = person-years

Figure 2. Kaplan Meir curves showing **[A]** time to onset of new diabetes mellitus (DM) and **[B]** cardiovascular disease (CVD)



ated with increased risk of DM when taken with low statin high adherence. As expected, male gender, increased age, and higher cardiovascular SCORE risk were also associated with increased risk of developing DM. Multi-regression analyses also showed that statin therapy at any adherence levels reduced the risk of CVD significantly. Again, as expected, male gender, increased age, higher BMI, raised cholesterol level, and high cardiovascular SCORE risk score were also associated with increased CVD risk.

DISCUSSION

Primary prevention randomized controlled trials (RCTs) [1,3] have shown that statin therapy with a range of LDL-C lowering capabilities reduces all-cause mortality and stroke compared to placebo in adults ≥ 40 years of age who have at least one risk factor for CVD. Other primary prevention RCTs also have shown that statin therapy reduces all-cause mortality [2,11-13]. Thus, common practice for primary prevention has been to treat subjects with risk factors with statin therapy aimed at lowering LDL-C to below 2.59 mmol/L.

Several studies, two meta-analyses, and a task force of the National Lipid Association have tried to reconcile the benefits of statins with the risk of developing DM and concluded that the modest increased risk of DM is more than offset by a reduction in cardiovascular events [4,11-18]. One study reported a 363% increased risk of DM after 15–20 years of statin exposure [19]. These results have led the U.S. Food and Drug Administration to publish a safety warning that statins might elevate blood sugar and HbA1C [20], and a requirement that statin manufacturers study and disclose this risk.

The mechanism of statin-induced DM and its effects on cardiovascular disease is complex and several mechanisms have been proposed [21], including decreased insulin secretion due to inhibition of glucose-induced Ca^{2+} signaling in β cells, decreased expression of glucose transporter type 4 possibly by reduction of insulin signal transduction via inhibition of necessary phosphorylation events, as well as alteration of cellular distribution of small G proteins, inhibition of adipocyte differentiation leading to a decrease in secretion of adiponectin and leptin, statin-induced decreased expression of mitochondrial uncoupling protein 3, and increased expression of microRNA.

In Israel, statin treatment for the prevention of both primary and secondary CVD has been common practice since 2000. A previous retrospective, population-based study of 230,000 MHS members on the effect of statins for primary and secondary prevention showed that statins were effective in decreasing cardiovascular mortality and that adherence and length of treatment were important in prevention of cardiovascular morbidity [22].

In the present study, we aimed to examine the risk of developing DM among patients who were treated with statins for primary prevention of CVD and to assess this risk in groups with a risk of developing CVD according to the SCORE modified for Israel. Half of the subjects had a low cardiovascular risk at baseline and a quarter had a moderate risk. As expected, the SCORE risk increased according to age, BMI, hypertension, and total cholesterol. New cases of DM and CVD occurred in approximately 4% and 2%, respectively, of subjects during the 5 year follow-up period. Statin therapy was used by 17.9% of the study population. The incidence of both CVD and DM increased as the cardiovascular SCORE risk increased (RR 9 and 3.8, respectively, for the lowest and highest risk groups). Adherence to statins, as assessed by pharmacy purchase data, correlated with increased DM and decreased cardiovascular risk.

Normal weight individuals were at a higher risk of DM than overweight or obese patients at all treatment intensities and adherence levels. A possible explanation is that in high-risk overweight patients, the potential to develop DM had already

been realized before initiation of statin therapy. Of note, in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [5], no correlation was found between being overweight and the development of DM.

Statin therapy in the present study was associated with a reduced CVD incidence in patients with a high baseline cardiovascular SCORE risk when used at high, moderate, or low intensities and at different adherence levels. However, the associated risk of developing DM increased with all intensities. Therefore, the decision whether to treat a patient with statins should take into account not only the specific benefit for reducing CVD but also the specific risk for developing DM:

PATIENTS AT LOW CVD RISK

The balance is in favor of avoiding statin treatment in low doses. These patients have no cardiovascular protective benefit from statins, and in this group the NNH for DM with low intensity statin regimens was 40. These findings are in accordance with the ACC/AHA guidelines [8] and the U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guidelines [23] in which low intensity treatment was not recommended for any of the cardiovascular risk groups.

PATIENTS AT HIGH CARDIOVASCULAR SCORE RISK

The NNT in our cohort was 29 and the NNH was 200. These figures clearly support previous studies and guidelines that recommend treatment of high cardiovascular risk patients with statins despite a certain risk for DM.

PATIENTS WITH MODERATE CARDIOVASCULAR SCORE RISK

Our results need to be considered with caution. In patients with moderate cardiovascular SCORE risk levels, the NNT was 125 with an NNH of 50. The net effect seems to disapprove use of statin treatment in this group, in disagreement with previous articles and guidelines.

Our results therefore differ from those of Waters and colleagues [24], who suggested that the risk of developing DM is limited to patients who are already at high risk.

Of note, high intensity statin treatment was used by a very small proportion of our study population and therefore no comparison was performed between high and low intensities of statin therapy regarding the association with incidence of DM.

STUDY STRENGTHS AND LIMITATIONS

The present study is one of the largest studies undertaken on the risk of statin therapy on the development of DM in community settings with respect to length of follow-up period and size of study population. Other strengths include the historical, prospective real-life analysis where the treatment decisions by the physicians were made without formal categorization of the cardiovascular risk of patient, use of administrative databases to avoid differential recall bias, and systematic and comprehensive collection of personal data, medical history, and study outcomes.

Several study limitations should be considered. First, our analysis was retrospective, allocation of therapy and dose was not randomized. Adherence was assessed by dispensing information, feasible for estimating medication use in large populations, yet does not ensure that the drug is actually consumed, perhaps leading to a non-differential information bias. However, it is reasonable to assume that for economic considerations, patients do not purchase medications consistently unless they use them. Second, adherence could be a surrogate for other unmeasured variables, reflecting higher quality of care. Third, long-term cardiovascular risk may require at least 8–10 years to reach the level of a CVD risk equivalent, thus the 5 year follow-up in our study might have underestimated both long-term benefit of statin risks as well as long-term effect of statin-induced DM and its subsequent cardiovascular risk. Forth, as 90% of the patients were prescribed low-dose statin regimens, we could not assess the effects of higher doses and explore a possible dose-response effect of statins on DM incidence. Furthermore, about two-thirds of the patients taking statins received simvastatin; therefore, we cannot speculate whether different statins convey different levels of DM-induced risk.

CONCLUSIONS

This study shows that the initial cardiovascular SCORE risk level is important in determining both the potential benefit of reducing cardiovascular risk and the potential risk of statin-induced DM. Our data supports use of statins in patients with high, but not low, cardiovascular SCORE risk. For patients with intermediate cardiovascular risk treatment, decision should be individualized based on family history and patient preferences.

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References

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-97.
2. 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.
3. 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.
4. 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.
5. 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.

6. Shechter M, Beigel R, Matetzky S, Freimark D, Chouraqui P. The intensive statin therapy myth. *IMAJ* 2005; 7: 683-7.
7. Zhang X, Hu D. [Comments for 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults]. *Zhonghua Nei Ke Za Zhi* 2015; 54: 9-12 [Chinese].
8. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129: S1-45.
9. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. *Pharmacoeconomics* 2004; 22 Suppl 3: 13-23.
10. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol* 2010; 63: 46-55.
11. 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.
12. Ray KK, Seshasai SR, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med* 2010; 170: 1024-31.
13. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; 1: CD004816.
14. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 364: 685-96.
15. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279: 1615-22.
16. Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N, The Diabetes Subpanel of the National Lipid Association Expert P. An assessment by the Statin Diabetes Safety Task Force: 2014 update. *J Clin Lipidol* 2014; 8: S17-29.
17. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 2008; 52: 1769-81.
18. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006; 368: 1155-63.
19. Macedo AF, Douglas I, Smeeth L, Forbes H, Ebrahim S. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice pesearch datalink. *BMC Cardiovasc Disord* 2014; 14: 85.
20. FDA Drug Safety Communication. Important safety label changes to cholesterol lowering statin drugs 2012. [Available from: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm] [Accessed: 2015].
21. Brault M, Ray J, Gomez YH, Mantzoros CS, Daskalopoulou SS. Statin treatment and new-onset diabetes: a review of proposed mechanisms. *Metabolism* 2014; 63: 735-45.
22. Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med* 2009; 169: 260-8.
23. Downs JR, O'Malley PG. Management of dyslipidemia for cardiovascular disease risk reduction: synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. *Ann Intern Med* 2015; 163: 291-7.
24. Waters DD, Ho JE, Boekholdt SM, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *J Am Coll Cardiol* 2013; 61: 148-52.

Capsule

Different species solve problems differently

The most powerful methods available for investigating the neural correlates of perceptual learning increasingly rely on rodents as animal models. The implicit assumption is that whenever rodents perform a task, they engage a similar neural circuitry as other species, such as primates. This is problematic for visual system studies because rodent vision is poor. **Mustafar** and colleagues examined the behavior of rats, long-tailed macaques, and tree shrews as they learned an identical visual discrimination task. Rats learned more slowly and had a lower peak performance than the other species. They also learned in a different way. Throughout training, including after acquisition, rats used reward history to guide their performance, unlike long-tailed macaques and tree shrews. These results indicate the necessity of careful comparative studies in translational research.

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Eitan Israeli

Capsule

Metabolic changes in gut surgery

Roux-en-Y gastric bypass surgery (RYGB) is an effective treatment strategy for obesity. Whether RYGB-mediated weight loss is directly associated with the long-term metabolic benefits remains elusive. **Ben-Zvi** and colleagues studied the physiological adaptations of obese mice subjected to RYGB or calorie restriction and compared the results with data for post-RYGB patients. RYGB-operated mice displayed beiging of adipose tissue and short-term skeletal muscle adaptations not observed in calorie-restricted mice. Meanwhile, altered amino acid metabolism in the liver and intestinal immune and metabolic changes were conserved between RYGB-operated mice and humans. These integrated organ adaptations exhibited a time-dependent pattern of activation coordinated with the circadian clock network, providing evidence that metabolic changes associated with RYGB are not attributable to weight loss alone.

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