Therapy and clinical trials

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The beginning of 2014 was punctuated by the publication of the long-awaited ACC/AHA Blood Cholesterol Guidelines [1]. Compared with ATP-III, this document expanded the estimated number of US statin-eligible adults from 43.4 to 56.0 million, with the majority (10.4 million) having no established cardiovascular disease (CVD), but an elevated 10-year atherosclerotic CVD event risk [2].

Each successive guideline has appropriately pushed for earlier and more aggressive implementation of statins. Although immediate medication use undoubtedly improves medical compliance, dietary modification could be becoming a forgotten tool. Diet was once touted as the initial strategy in lipid control, with medications limited to patients not achieving cholesterol targets. Although healthy lifestyle remains an instructional focus for all concerned physicians, how patients view such interventions in light of medications that can overcome their indiscretions remains unclear. A recent cross-sectional study examined calorie consumption in statin users from 1999 to 2010 as a part of the National Health and Nutrition Examination Survey [3▪▪]. Initially (1999 to 2000) calorie or fat intake was significantly lower in patients taking statins. Interestingly, the difference became insignificant in 2004 to 2005 and 2005 to 2006, and reversed in 2009 to 2010, when statin users had higher calorie or fat intakes. BMI was also higher in statin users, as was diabetes prevalence.

Several clinical trials over the past decade have identified an increased risk of diabetes for statin users [4,5]. In parallel with a previous meta-analysis [6], a large nested case-control observational study by the Canadian Network for Observational Drug Effect Studies investigators demonstrated an increased incidence of diabetes in patients newly treated with higher potency compared with lower potency statins for secondary prevention [7▪▪]. This was the first study to target incident diabetes as the primary outcome. Sensitivity analysis was used to eliminate the possibility of undiagnosed diabetes prior to statin therapy. Among 136 966 participants, 3629 patients developed diabetes within 2 years. Higher potency statins resulted in a 15% increased risk of diabetes, with the number needed to harm being 342. A recent reanalysis of the nateglinide and valsartan in Impaired Glucose Tolerance Outcome Research Study also found an association between statin use and new onset diabetes in high-risk patients with impaired glucose tolerance [8▪]. The hazard ratio was 1.32, and the number needed to harm was 12 for statins. Potency and dose were not assessed, however.

The means by which statins increase diabetes remain unclear, though several mechanisms have been proposed [9]. Statins may act on receptors in muscle or liver to promote insulin resistance. Hydrophilic and lipophilic properties of statins may also be involved. The role of changes in dietary patterns has yet to be formally explored.

Statins significantly reduce CVD morbidity and mortality, and these benefits undoubtedly outweigh the potential risks of diabetes [10▪]. However, clinicians should carefully consider dose and potency for each patient they prescribe statins. Vigilant diabetic screening and follow-up in high-risk patients may be beneficial. Although additional studies are likely to shed greater light in this area, physicians would be wise to preach for appropriate dietary modification in their statin-treated patients.

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Conflicts of interest

Dr Krasuski has served as a consultant to Actelion and Bayer. He is also on the scientific advisory board for Ventripoint.
Dr Chongthammakun has no conflicts of interest.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. 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 (25 Suppl 2):S1–S45.
2. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, *et al.* Application of new cholesterol guidelines to a population-based sample. N Engl J Med 2014; 370:1422–1431.
3. ■■ Sugiyama T, Tsugawa Y, Tseng CH, *et al.* Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins? JAMA Intern Med 2014; 174:1038–1045.

This was a cross-sectional study that assessed the caloric and fat intake in 27 886 United States adults from 1999 to 2010 through the National Health and Nutrition Examination Survey. There was a trend in the increased consumption of calories and fat in statin users over time, but not in nonusers. The information from this study should raise the awareness of diet control while on statin therapy, as dietary noncompliance could play a role in the development of diabetes in this patient population.

4. Rajpathak SN, Kumbhani DJ, Crandall J, *et al.* Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32:1924–1929.
5. Sattar N, Preiss D, Murray HM, *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375:735–742.
6. 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; 305:2556–2564.
7. ■■ Dormuth CR, Filion KB, Paterson JM, *et al.* Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ 2014; 348:g3244.

The purpose of this large cohort study involving 136 966 patients was to examine the correlation between statin potency and the risk of new onset diabetes. Higher potency statins, regardless of brand, were associated with a significantly increased risk of new onset diabetes in the first 2 years of statin initiation compared with lower potency statins [relative risk of 1.15, 95% confidence interval (CI) 1.05 to 1.26]. Further studies are needed to clarify the mechanisms that are responsible for this observation.

8. ■ Shen L, Shah BR, Reyes EM, *et al.* Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study. BMJ 2013; 347:f6745.

NAVIGATOR was an international, randomized, double blinded, placebo-controlled trial that primarily investigated whether valsartan and nateglinide reduced the incidence of diabetes and cardiovascular events in high-risk patients with impaired glucose tolerance and other cardiovascular risk factors. Further analysis demonstrated that diuretics and statins were associated with increased incidence of new onset diabetes, whereas beta-blockers and calcium channel blockers were not.

9. Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol 2011; 22:460–466.
10. ■ Wang KL, Liu CJ, Chao TF, *et al.* Risk of new-onset diabetes mellitus versus reduction in cardiovascular events with statin therapy. Am J Cardiol 2014; 113:631–636.

The diabetogenic risk of statins was shown to be dose-dependent in this propensity score-matched cohort of prediabetic patients treated with statins. However, the clinical benefits of statin in the reduction of cardiovascular events and mortality (hazard ratio 0.70, 95% CI 0.61-0.80) outweighed the risks of developing new onset diabetes (hazard ratio 1.20, 95% CI 1.08-1.32).

FURTHER RECOMMENDED READING

Ong KL, Waters DD, Messig M, *et al.* Effect of change in body weight on incident diabetes mellitus in patients with stable coronary artery disease treated with atorvastatin (from the treating to new targets study). Am J Cardiol 2014; 113:1593–1598.

This analysis from the Treating to New Targets study that randomized 7595 patients with stable coronary disease to high-dose and low-dose atorvastatin found that weight gain during the first year of statin therapy was an independent predictor of new onset diabetes. This finding emphasizes the clinical value of weight control as well as lifestyle changes in the prevention of statin-induced diabetes. In addition, high-dose statin groups had 14% increased risk of developing diabetes as compared with low-dose statin-treated patients in this study, though this difference was not statistically significant.

Lee DS, Markwardt S, Goeres L, Lee CG, *et al.* Statins and physical activity in older men: the Osteoporotic Fractures in Men Study. JAMA Intern Med 2014. [Epub ahead of print]

Statin users had less physical activity than the nonusers in this prospective observational study in older men. This effect persisted throughout the time that patients remained on statin therapy. This is of concern, given that sedentary behavior has a known association with cardiovascular mortality, which may be even more pronounced in high-risk conditions (such as diabetes).

Henriksbo BD, Lau TC, Cavallari JF, *et al.* Fluvastatin causes NLRP3 inflammasome-mediated adipose insulin resistance. Diabetes 2014. [Epub ahead of print]

This study proposes a new mechanism to explain the diabetogenic effect of statins. Fluvastatin was observed to promote insulin resistance in the adipose tissue of obese mice through the activation of the NLRP3/caspase-1 pathway. Interestingly, the effect was inhibited by glyburide administration. It is currently unclear whether this also occurs in humans; and considerable investigation will be necessary to determine the risks/benefits of therapeutic interventions targeting insulin resistance in high-risk patients taking statins.