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REVIEW ARTICLE

Statin in Diabetes – Good or Bad

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Abstract: *Over the last three decades, statins have played a major role in primary and secondary prevention of cardiovascular morbidity and mortality. Recently there have been concerns about a possible association between statin use and new onset diabetes. However the cardiovascular benefits of statins have been found to outweigh any potential detrimental effects on glucose metabolism and diabetes risk and thus should not be denied to moderate- and high-risk patients. The different lipids guidelines for patients with type 2 diabetes mellitus are not in consensus and thus clinicians need to exert clinical discretion when deciding on which guideline to follow.*

Keywords: *guidelines, new-onset diabetes, statin.*

Introduction

Ever since the introduction of statins, the 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in 1982, their ascent to glory has been remarkable. Not only did they successfully decrease lipids, they were also found to be associated with many pleiotropic effects like decreasing LDL-C oxidation, enhancing the stability of atherosclerotic plaques, inhibiting vascular smooth muscle proliferation and platelet aggregation, reducing vascular inflammation, and many beneficial effects on endothelial function and blood flow.[1] Over the last two decades, multiple clinical trials have demonstrated the beneficial effects of statins in the reduction of cardiovascular event rates. Statin therapy has been associated with 25–45% reduction in cardiovascular events.[2] Primary prevention trials like ASPEN,[3] CARDS,[4] ASCOT LLA,[5] etc. have shown relative risk reduction of 8–34% in the 10-year risk for major CVD events in patients with diabetes while secondary prevention trials like CARE DM,[6] TNT DM,[7] 4S DM[8] have shown relative risk reduction of 13–50%. Such strong, clinically meaningful evidence in their favor have resulted in statins being the most widely prescribed drugs in the world. Recently, however, these molecules which have even been heralded as miracle drugs have come under question because of the unrevealing of an association of new onset diabetes (NOD) with statin use.

Statin and New Onset Diabetes

The interest in the association between statins and NOD was first observed by the West of Scotland Coronary Prevention Study (WOSCOP) 2001, which demonstrated a 30% risk reduction for incident diabetes with the use of 40 mg of pravastatin.[9] Subsequent trials of simvastatin,[10,11] pravastatin,[12–15] and atorvastatin,[16] however, failed to reciprocate similar results. Interest in this association was reignited in 2008 when a completely contrasting picture was presented by the Justification for the Use of Statins in Primary Prevention: an intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which reported increased incident of diabetes among patients taking rosuvastatin. In individuals with one or more risk factors, statin allocation was associated with a 28% increase in diabetes.[17] In the aftermath of the JUPITER report, a number of placebo-controlled and standard care-controlled trials of statin therapy have provided conflicting reports regarding statin use and NOD. Sattar *et al*. in a meta-analysis from 13 individual studies[9–21] (involving a total of 91,140 patients) concluded that statin therapy was associated with a 9% increased

risk for NOD (OR 1.09).[22] In another meta-analysis by Rajpathak and colleagues, including 57,593 patients from six trials (WOSCOPS,[9] ASCOT-LLA,[5] JUPITER,[17] HPS,[11] the Long-term Intervention With Pravastatin in Ischaemic Disease [LIPID] study,[19] and the Controlled Rosuvastatin Multinational Study in Heart Failure [CORONA][23]), a small increase in risk for type 2 diabetes was shown (relative risk 1.13, 95% confidence interval 1.03–1.23).[24]

Whether this effect of statins is a class effect or do other factors have implications in this association between statins and diabetes is another area of interest. Yamakawa *et al*. in a retrospective analysis, while examining the effect of atorvastatin 10 mg/day, pravastatin 10 mg/day, and pitavastatin 2 mg/day on glycemic control over 3 months, found that while random blood glucose and hemoglobin A_{1c} levels were increased in the atorvastatin group it was not affected in the other two.[25]

Another meta-analysis by Navarese showed the differential effect of different statins and their doses in the development of NOD.[26] Corrao *et al*. found that compared to patients with very low adherence (PDC <25%) to statin therapy, those with high (75%) adherence had a 32% increase risk of NOD.[27] Chen *et al*. found that the risk of statin-related NOD was cumulative-dose dependent and more evident for women aged 40–64 years compared to women aged 65 or more.[28] Preiss and colleagues in a meta-analysis of 32,752 patients in five trials found that higher potency statins were associated with a 12% increased risk of diabetes relative to lower potency statins (odds ratio 1.12, 1.04–1.22).[29] In contrast, a review by Yousef *et al*. of the EFFECT study did not find a higher diabetes mellitus risk with more intensive statin therapy based on the magnitude of LDL-C reduction.[30] One hypothesis states that lipophilic statins can passively penetrate extrahepatic tissues leading to myopathy and consequent insulin resistance, and it also decreases insulin secretion due to increased HMG-CoA inhibition or cytotoxicity.[31] However, the strong association between rosuvastatin, which is hydrophilic, and NOD goes against this hypothesis.

In the wake of these trials and the analyses reports, the US Food and Drug Administration (FDA) updated the labeling of statin medications in February 2012 incorporating a warning against a possible increased diabetes risk.

Mechanism of New Onset Diabetes with Statin Use

Several mechanisms have been proposed to explain the association between statin and NOD – direct, indirect or combined effects on calcium channels in pancreatic β-cells, reduced translocation of glucose transporter 4, decreases in downstream products such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and dolichol leading to reduced intracellular signaling, interference with intracellular insulin signal transduction pathways via inhibition of necessary phosphorylation events and reduction of small GTPase action, inhibition of adipocyte differentiation leading to decreased peroxisome proliferator activated receptor gamma and CCAAT/enhancer-binding protein, decreased leptin causing inhibition of β-cells proliferation and insulin secretion and diminished adiponectin levels.[32] However present evidence is not enough to definitively establish the strength of the cause–effect relationship of any of these proposed mechanisms. Elucidation of the mechanism may help identify preventative or therapeutic approaches to this problem.

Benefit Versus Risk

These findings create a paradox whereby the required statin therapy while representing the strongest cardiovascular risk reduction tool in diabetics, may be withheld to avoid excess risk of diabetes. Several reviews have tried to analyze whether this necessitates reduction in the use of statins, which have become an almost integral part of the diabetes treatment armamentarium. It must be understood that most of these meta-analyses, which showed the positive association of statins with diabetes, incorporated trials that were not designed to assess NOD, included studies with no FPG data after baseline (HPS, CORONA), and included patients who had underlying risk factors for diabetes like metabolic syndrome, mean elevated BMI, history of CVD and hypertension (ASCOT-LLA, JUPITER, LIPID, PROSPER, 4S, ALLHAT-LLT). Waters *et al*. found that those who had none or one of the risk factors for diabetes (impaired fasting glucose, obesity, elevated triglycerides, and hypertension) had no difference in the rate of NOD with either moderate or intensive statin therapy, but the risk was pronounced in those who had three or four risk factors.[33] In the JUPITER analyses in patients who did not have CVD at baseline, for every 54 new cases of diabetes in follow-up, 134 cardiovascular events or deaths were prevented. Those who had one or more risk factors for diabetes at baseline (MS, IFG, obesity, or HbA_{1c} > 6%) had a 39% reduction in the primary end point with a 28% increase in new diabetes, while those who had none of these risk factors had a 52% lower rate of cardiovascular events but no increase in diabetes. In the Sattar *et al*. analyses, in every 255 patients treated with statins over 4 years, for each 39 mg/dL reduction in LDL, there were 5.4 fewer deaths from CHD and cases of nonfatal MI with the risk of developing one additional case of diabetes. Also, among the 13 trials which reviewed the incidence of diabetes varied substantially, with only JUPITER and PROSPER showing statistically significant increase in rates (26% and 32%, respectively) while 4 had nonsignificant trends toward lower incidence and the remaining 7 had nonsignificant trends toward higher incidence. The Preiss *et al*. analyses

showed that for every 1000 patient-years, there were 6.5 fewer first major cardiovascular events and 2 more cases of diabetes in the intensive dose statin users. An analysis of 345,000 patients in the Veteran Affairs Healthcare System indicates that, after adjustment for age and use of aspirin, β-blockers, and angiotensin-converting enzyme inhibitors, the statin-attributable change in fasting plasma glucose was 2 mg/dL (7 mg/dL increase, vs. 5 mg/dL in nonstatin users, $P < 0.0001$) for nondiabetic users and 7 mg/dL (39 mg/dL increase, vs. 32 mg/dL in nonstatin users, $P < 0.0001$) for diabetic users.[34] In a recent analysis, Wang *et al*. found that over more than 7 years of follow-up of statin therapy, the risk of DM was increased by 15% with a significant 18% reduction in the risk of myocardial infarction, a significant 9% reduction in the risk of major adverse cardiac events, and a 39% lower risk of in-hospital mortality.[35] That the glucose changes seen on statin therapy may not extrapolate to an equivalent increase in adverse cardiovascular events as seen in other diabetic patients was shown by Waters *et al*. While evaluating three trials of high-dose atorvastatin therapy, they found that major cardiovascular events occurred in 11.3% of those with NOD, 10.8% of those without NOD, and 17.5% of those who had diabetes at baseline.[33] These analyses, while acknowledging an increased diabetes risk with statin use, agree in principle that the concern surrounding the diabetogenic effects of statins appears small in comparison with the favorable benefit-to-risk ratio associated with their use in diabetics and nondiabetic patients with moderate to high cardiovascular risk. It is only the lower risk individuals who perhaps may represent a group in which the benefits of therapy do not outweigh the potential risk of incident diabetes. The Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT) to evaluate the effect of a statin on the onset of diabetes as the primary end point, which is expected to be completed in 2015, will hopefully throw some more light into this issue and increase our understanding of the statin–diabetes association.[36]

Use of Statin in Type 2 Diabetes Mellitus

In view of the benefits associated with statin therapy, the ADA has advocated statin therapy to all diabetics with overt cardiovascular disease keeping a LDL-C target as <70 mg/dL. In those without overt cardiovascular risk, statin therapy is recommended if the age is more than 40 with any one of the CVD risk factors (family history of CVD, smoking, hypertension, dyslipidemia, or albuminuria) keeping an LDL target of <100 mg/dL.[37]

The American College of Cardiology and American Heart Association have released new guidelines in 2013 for treating high blood cholesterol to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) in adults.[38] They have endorsed the introduction of a risk calculator based on which 10-year CVD risk as well as the lifetime risk of an individual can be calculated. As per these guidelines for those with diabetes between 40 to 75 years of age, moderate-intensity statin therapy is recommended for all and high-intensity statin therapy is recommended for those with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. In adults with DM, who are <40 years or >75 years of age, it is recommended to evaluate the potential for ASCVD benefits and for adverse effects, for drug–drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.

What has changed from the previous NCEP ATP III guidelines is that treatment goals for LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) are no longer recommended, high-intensity and moderate-intensity statin treatment is emphasized, while low-intensity statin therapy is nearly eliminated and nonstatin therapies have been markedly de-emphasized with no guidelines for the treatment of high triglycerides. The guidelines choose to ignore the residual risk in patients on both moderate- and high-intensity statin therapy and remain noncommittal about patients with recurrent cardiovascular events already on maximal tolerated statin doses.

The guidelines which came after a considerable number of years after ATPNCEP III has generated a lot of controversies. AACE has declined to endorse the new guidelines criticizing the database considered which according to them omits much new information. AACE along with many other apex bodies also disagrees with removal of the LDL targets and the concept that statin therapy alone is sufficient for all at-risk patients. The most criticized aspect of the guidelines remains the overt importance attached to the risk calculator. When analyzed in recent cohorts (Women's Health Study, Health Study, and Women's Health Initiative) the new calculator overestimates the 10-year risk of ASCVD by 75–150%. This raises concern of overt treatment of many patients at low risk. In contrast the risk calculator relies heavily on age and sex and does not include other factors such as triglyceride level, family history, BMI, C-reactive protein, or lipoprotein(a) and thus could deny the benefits of statin treatment to many patients at substantial risk. The new AHA/ACC guidelines with its elimination of targets, drawbacks of the risk calculator, and institution of aggressive therapy independent of LDL levels are a marked deviation from the previous lipid guidelines and contemporary diabetes guidelines and remain to be validated. In view of these shortcomings of the AHA/ACC guidelines, it has been suggested to exert caution in strict adherence to the new guidelines and instead to consider a hybrid of the old guidelines (using the ATP III LDL-C goals) and the new ones (emphasizing global risk assessment and high-intensity statin treatment).[39]

Recently the draft guidelines for The National Institute for Health and Care Excellence (NICE) have been published.

NICE has recommended estimating the level of risk using the QRISK2 assessment, starting high-intensity statins for the primary prevention of CVD in patients with a 10-year risk of 10% or more with atorvastatin 20 mg, secondary prevention with atorvastatin 80 mg, and a treat to target of 40% reduction in non-HDL-C.

Conclusion

When assessed at the backdrop of the immense benefit of statins in terms of reduction in cardiovascular mortality and morbidity, the relatively small but significant risk of NOD does not appear enough to withhold therapy in deserving patients. Rather these patients may be monitored more vigorously for early detection of new onset hyperglycemia. Different guidelines differ in their recommendations for the use of statins in diabetes and it needs to be re-emphasized that guidelines are meant to be an expression of expert recommendations and not to dictate practice, wherein lies the importance of individual discretion in exerting clinical judgment, weighing of potential pros and cons, considering drug–drug interactions and patient preferences before deciding on which recommendation to follow.

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