**The Statin Diabetes Conundrum: Short-term Gain, Long-term Risk or Inconvenient Truth?**

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|Disclosures

Evid Based Med. 2015;20(4):121-123.

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**Abstract and Introduction**

**Abstract**

Statin drugs have become the mainstay of many cardiovascular disease prevention guidelines and are recommended for most adult patients with diabetes. A careful review of the evidence, however, suggests that the clinical benefits of statins in diabetes may have been overstated by relying on meta-analyses that incorporate randomised controlled trials (RCTs) neither designed nor powered to assess the effects of statins in diabetes. Multiple RCTs specifically designed and powered to study the effects of statins in diabetes have demonstrated inconsistent clinical benefits and no mortality benefit. The conclusions of these meta-analyses should not supersede the results of these large, well-conducted RCTs. Reports that conclude that the benefits of statins outweigh the risks have probably underestimated the long-term risks of statin exposure and the deleterious consequences of long-term diabetes.

**Introduction**

The interplay of diabetes mellitus, statin drugs and cardiovascular disease is extremely complex.[1] The recent finding that statin drugs may cause diabetes, and the US Food and Drug Administration requirement that statin manufacturers disclose this risk has led to numerous reports, studies, reviews and commentaries. The consensus opinion is reassuring—there is a modest increased risk of diabetes from statin drugs, but the benefits outweigh the risks in appropriately selected patients.[2] Most perplexing is the fact that one study suggests statins may protect against diabetes (WOSCOPS) while others suggest statins may cause diabetes.[1] Before clinicians accept this consensus view it may be constructive to review the evidence behind current guidelines and recommendations.

**Diabetes as a Coronary Heart Disease Risk Equivalent**

It is widely acknowledged that diabetes mellitus is a major risk factor for the development of coronary heart disease (CHD) and many refer to diabetes as a CHD risk equivalent. This conclusion is largely based on a 1998 study where patients with diabetes appeared to have a risk of future myocardial infarction comparable to patients without diabetes but with a prior history of myocardial infarction.[3] Often overlooked is the fact that the mean diabetic disease duration was approximately 8.1 years. Further investigations have demonstrated that cardiovascular risk correlates with the duration of diabetes, not simply the onset or diagnosis of diabetes.[4,5] It appears likely that the risk of future CHD does not reach the level of a CHD risk equivalent until the diabetic disease duration is at least 8–10 years.[1] Clearly, not all people with diabetes share the same risk of future CHD and not all should be labelled as having a CHD risk equivalent. This conclusion is especially germane when one examines more recent studies of statin use in diabetes.

**Mortality Is More Important Than Combined Clinical End Points**

Over the past 20 years, the primary end point of many randomised controlled trials (RCTs) of statins has shifted from total mortality to combined clinical end points. The use of combined end points may unfortunately engender a unique set of problems.[6] The perceived benefit of a RCT using combined clinical end points may be exaggerated by assigning equal importance to disparate clinical events such as a hospital admission for angina and death from a heart attack. Not all studies utilise the same clinical end points, and often there is discordance between a perceived clinical benefit and a lack of mortality benefit. This paradox is illustrated by the Cholesterol Treatment Trialists' (CTT) meta-analysis of 27 RCTs of statin therapy in people at low risk of vascular disease.[7] This CTT analysis clearly showed a significant benefit in terms of combined clinical end points, but when a separate meta-analysis of the same 27 studies was performed there was no mortality benefit.[8] Similarly, CTT performed a meta-analysis of 14 RCTs of statins in diabetes and concluded there was a robust reduction in all vascular events (rate ratio 0.79, 99% CI 0.72 to 0.86; p<0.0001), but the mortality benefit was quite modest (rate ratio 0.91, 99% CI 0.82 to 1.01; p=0.02).[9]

**Meta-analysis Versus RCTs**

Current guidelines recommend that most adults with diabetes should be treated with a statin drug irrespective of the duration of diabetes.[10] This recommendation is based in part on the results of the CTT diabetes meta-analysis.[9] Although meta-analyses can provide an efficient and accurate way of integrating the results of multiple clinical trials, the hazards of meta-analysis are well described and some refer to meta-analysis as 'the alchemy of the 21st century'.[11,12] Consider that this CTT meta-analysis demonstrated a mortality benefit even though 9 of the 12 individual studies with mortality results reported no mortality benefit (WOSCOPS, Post-CABG, GISSI-P, LIPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, ALERT, CARDS). There are a number of possible explanations for this discordance. First, many of these studies were not powered to show mortality differences. The CTT meta-analysis also weighted these studies according to the degree of low-density lipoprotein lowering rather than the size of the study population. Furthermore, the CTT meta-analysis did not include two large RCTs specifically designed and powered to assess the effect of statins in diabetes (ASPEN and 4D). Finally, a separate systemic review with more stringent study selection criteria concluded that there is no benefit (clinical or mortality) of statins in diabetes.[13]

The conclusions of meta-analyses may also contradict the results of large, well-conducted RCTs. In one investigation, the results of 19 meta-analyses failed to accurately predict the results of 12 large RCTs in 35% of studies.[14] Similarly, the favourable results of the CTT meta-analysis of statin use in diabetes are discrepant with the lack of clinical benefit noted in two large RCTs of statins in diabetes. In the ASPEN trial 2410 people with type 2 diabetes were randomised to either atorvastatin 10 mg/day or placebo and no benefit in total mortality or combined clinical end points was seen after 4 years.[15] The 4D study randomised 1255 people with type 2 diabetes on dialysis to either atorvastatin 20 mg/day or placebo for approximately 4 years and also demonstrated no benefit in either total mortality or combined clinical end points.[16] However, this lack of statin benefit in dialysis patients with diabetes may be attributable to the complex pathophysiology of renal failure and dialysis, and perhaps should not be extrapolated to patients with diabetes not on dialysis. Nevertheless, to better understand this discordance it is instructive to examine the individual studies utilised in the CTT meta-analysis. Of the 14 RCTs included, only 1 (CARDS) was specifically designed and powered to look at the effect of statins in diabetes.[17] The remaining 13 studies were not specifically targeted at people with diabetes, but the results in patients with diabetes were extracted as part of a subgroup analysis.[9] Although subgroup analyses can provide valuable information, they can also give rise to misleading results.[18] Curiously, the one study (CARDS) that did specifically target patients with diabetes showed a benefit in the combined clinical end point but not in total mortality (p=0.059).[17] This discordance between CARDS showing a clinical benefit, and ASPEN and 4D not demonstrating a clinical benefit may be related to the duration of diabetes. As previously stated the duration of diabetes correlates with the risk of future CHD. CARDS enrolled patients with diabetes duration of at least 6 months whereas the diabetes duration in ASPEN was at least 3 years, and in 4D the average diabetes duration was approximately 18 years. Therefore, CARDS likely enrolled patients with diabetes at much lower risk and these results may not be applicable to higher risk patients with diabetes. While some biostatisticians will debate whether meta-analyses or large RCTs are the gold standard, clinicians will have to use their own judgement to make sense of these contradictory results.

**Does the Statin Benefit Outweigh the Risk of Diabetes?**

Several authors, 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 diabetes. Each has concluded that while there is a modest increased risk of developing diabetes, the number of new cases of diabetes is more than offset by a reduction in cardiovascular events.[2,19,20] On the surface this conclusion seems logical, but it fails to incorporate the effect of time. Since many patients are prescribed life-long statin therapy, the consequences of long-term exposure are extremely important. Consider first that these analyses included studies of short duration, generally less than 5 years, whereas longer statin exposure may lead to an even higher risk of diabetes. One study that has provided long-term data reported a 363% increased risk of diabetes after 15–20 years of statin exposure.[21] Another reported a 46% greater risk of type 2 diabetes mellitus with statin therapy among patients with the metabolic syndrome followed for 5.9 years.[22] Second, the risk of CHD in diabetes is progressive. The long-term cardiovascular risk is high in nearly all patients with type 2 diabetes mellitus, but may require at least 8–10 years to reach the level of a CHD risk equivalent.[1] Consequently, published analyses that examine the risks and benefits of statins in diabetes over the short-term may not provide an accurate assessment of the long-term consequences. Conversely, longer-term cholesterol lowering with statin therapy may provide even greater benefit, as suggested by Mendelian randomisation studies.[23] Nevertheless, by failing to incorporate the impact of time, many analyses may have underestimated both the risk of developing diabetes and the subsequent hazards of cardiovascular events.

The statin diabetes conundrum forces medical providers to make clinical decisions based upon incomplete data. I believe the full effect of statins in diabetes and the risk of statin induced diabetes has been obfuscated by focusing upon short-term observations, combined clinical end points, and meta-analyses while quietly overlooking the lack of mortality benefit demonstrated in multiple well-conducted RCTs. To some degree this lack of mortality benefit can be explained by the fact that many studies were neither designed nor powered to demonstrate a mortality advantage. Alternatively, it is also possible that there simply is no mortality benefit of statins in diabetes.

The statin-centric approach to preventing CHD may distract us from other therapies of proven benefit. Specifically, the Mediterranean diet has consistently been shown to both reduce CHD mortality and reduce the risk of developing type 2 diabetes mellitus. The statin diabetes conundrum may only be resolved by long-term RCTs but, until then, we must acknowledge that the evidence to support the use of statins in diabetes is inconsistent and the long-term risks of statins may have been under-appreciated.