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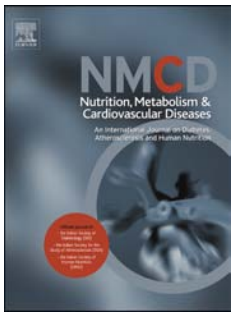

Putting the diabetes risk due to statins in perspective: A re-evaluation using the complementary outcome

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Viewpoint

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ABSTRACT

Aims: Statins are used extensively to treat dyslipidemia and have been associated with significant clinical benefit that increases with dose. However, recent studies have associated statins with an excess risk of developing diabetes mellitus, which may offset the clinical benefit to patients. Adverse events related to intensive-dose statin therapy were revisited in light of recent data regarding the use of relative risks.

Data Synthesis: A meta-analysis was replicated with the event of interest redefined as the complementary outcome (no-onset of diabetes). Five randomized controlled trials that compared the risk of intense-dose with moderate-dose of statin therapy for the onset of diabetes with a follow-up greater than 12 months were included in the analysis. A reduction in the risk for no-onset of diabetes was found when intensive-dose statin therapy was compared with moderate-dose statin therapy, revealing a relative risk of 0.9908 (95%CI: 0.9849-0.99679). Over two years, one more patient was harmed by diabetes onset for every 237 patients exposed to intensive-dose statin therapy (95%CI: 123 - 3847) compared with standard dose statin therapy.

Conclusions: Statins are associated with only a very small increase in risk of diabetes mellitus. Previous research selected the outcomes with the lower baseline risks and therefore the actual risk associated with statins has been largely over-estimated.

INTRODUCTION

Statins are used extensively to reduce low-density lipoprotein cholesterol and have been associated with significant benefits in patients with coronary artery disease, including a reduced risk of myocardial infarction, stroke, and death (1). Several trials have recently demonstrated that these benefits are greater with an intensive statin regimen which has been shown to reduce the risk of cardiovascular events and death beyond that of the standard (moderate dose) statin regimen (2; 3). However, there is growing concern that the protective properties of statins may be offset by non-cardiovascular safety concerns and moreover, that this risk of adverse events may also be greater with intensive-dose statin therapy compared with a standard regimen (2).

The main adverse event of concern is the previous suggestion that statin therapy can be associated with approximately a nine percent higher risk of developing diabetes mellitus compared with placebo or standard care (4-6), and this risk appears to be dose dependent (7). A meta-analysis by Preiss et al. compared intensive-dose with moderate-dose statin therapy and reported a 12% increase in the odds (OR=1.12) of incident diabetes among patients assigned to intensive-dose statin therapy compared with a standard dose (7). Our concern was that these risks may have been magnified by the mathematical peculiarity whereby the odds ratios (ORs) and relative risks (RRs) are inflated when event rates are low (8). We therefore undertook the present study to re-analyse the meta-analysis by Preiss et al. utilising the complementary outcome of non-events for which the event rates were higher, and provide clarification with regards to the safety implications of statin treatment.

METHODS

Five randomised controlled trials (RCTs) that compared the risk of diabetes onset with intensive-dose and moderate-dose statin therapy were included in the replication of the meta-analysis by Preiss et al. (7).The event of interest was redefined as the complementary outcome with the higher baseline risk, which was no-onset of diabetes. In selecting the outcome with the higher baseline risks, the mathematical anomaly by which the RRs are magnified at lower baseline risks was avoided (8). In addition, the RRs were reported rather than the ORs as the effect size of the intervention because magnification occurs at both ends of the risk spectrum for the OR while it only arises at the lower end of the risk spectrum for the RR (8).

The risk difference (RD) at two years follow-up was also computed by estimating the events based on the yearly incidence rate of the complementary outcome in each RCT. For these studies of duration more than two years, the yearly incidence rate (IR) was estimated as $IR = -[\ln(1 - CI_t)/t]$ where CI_t is the cumulative incidence proportion of events at the end of the study and t is the duration of follow-up (9). The two year cumulative incidence was then computed as $1 - e^{-IR(2)}$. In addition to the RD, the number needed to harm (NNH) and the number needed to treat (NNT) were computed based on the computed RD at two years.

Heterogeneity was considered present if tau squared (τ^2) > 0 (10) and this was chosen over I^2 or the P value on Cochran's Q as the most sensitive indicator of heterogeneity. It may be pointed out that both τ^2 and I^2 are derived from Cochran's Q and thus these indices mostly concur albeit with varying degrees of sensitivity. The RCTs included were found to be homogeneous, thus the fixed effects model (inverse variance) was used to pool the effect estimates. This however is identical to the random effects model used by Preiss et al. (7) given the lack of heterogeneity across studies. The analysis was done using MetaXL version 1.4 (http://www.epigear.com).

RESULTS

Table 1 presents the number of non-events (no-onset of diabetes) from the five RCTs. Table 2 presents the RRs as well as the RD (at two years follow-up) for each RCT along with the pooled effect size for no-onset of diabetes. Results indicate a 0.92% (RR 0.9908; 95%CI: 0.9849 - 0.9968) reduction in the patients remaining free of diabetes when exposed to intensive-dose compared with moderate-dose of statins. This also suggests a 0.92% risk increase in diabetes onset if moderate-dose statin therapy were to be changed to intensive-dose statin therapy. The RD and NNH at 2 years were statistically significant and suggest that one more patient more develops diabetes for every 237 patients exposed to intensive-dose statin therapy over two years (95%CI: 123 – 3847). To compare results, had we used diabetes onset as the outcome of interest, the pooled RR would have been 1.11 similar to the odds ratio of 1.12 reported by Preiss et al suggesting a 11% increase in incident diabetes. This is a much greater increase in risk than the 0.9% increase based on the complementary outcome we report above.

DISCUSSION

The aim of this study was to clarify the safety profile of statin therapy using a contemporary method of risk assessment that accounts for the inflation of risk with low event numbers. The present study revealed an extremely low risk of diabetes mellitus with intensive-dose statin therapy when compared to reports that use the complementary outcome (incident diabetes). Specifically, the RR estimate for risk of no-onset of diabetes was low, with a relative risk of 0.9908. This suggests only a 0.9% increase in risk of new diabetes onset when patients are moved from moderate to intensive-dose of statin therapy which clearly diverges from the 11-12% (RR=1.11; OR: 1.12) increase in risk or in odds as reported by Preiss et al. (7). A weak (but statistically significant) association with diabetes onset was thus evident when evaluating intensive-dose statins compared with moderate-dose statin therapy and therefore the magnitude of the results conflict with previous research that demonstrates a larger effect on diabetes onset. Based on these results, the clinical benefit of statin therapy may not be offset by diabetes concerns and in fact, based on the benefits on the vascular endothelium that go beyond the cholesterol lowering effect (11; 12) and the established benefits of intensive statin therapy compared with moderate doses in preventing cardiovascular events (13), these findings suggest that the increased risk of diabetes may not be large enough to counter its benefits. It is worth mentioning that akin to Preiss et al. our objective was to analyse the risk of intensive-therapy statin on onset of diabetes mellitus (outcome-Y); however, no-onset of diabetes was selected (outcome not-Y) for the analyses since it was the outcome with the higher baseline risk. By selecting the outcome with the higher baseline risk (in this case outcome not-Y) the artificial magnification of the effect size of the RR reported by Preiss et al. was avoided. Therefore, the selection of the RR in future studies should be based on the outcome with the higher baseline risks and not on the study design.

In absolute terms, the differences between the intervention and control groups for the statin analyses were statistically significant. One more patient is harmed by diabetes onset for every 237 patients exposed to intensive-dose statin therapy over two years compared to the moderate dose strategy. Given that the treatment effect in terms of cardiovascular prevention in previously reported studies is large (14; 15) and statin intervention has been well documented to reduce cardiovascular events and prevent death (16), this benefit will not be offset by the very small risk of onset of diabetes.

It is clear based on the results that reclassification of the event as the outcome with higher baseline risk (no-onset of diabetes) has put the RR into perspective and thus avoided the mathematical exaggeration of the RR that occurs with lower baseline risks (8). Nevertheless, there is still a risk documented, albeit small. This warrants further research to determine the mechanism of this effect so that patients at risk can be identified and offered alternative therapies. The issue of reporting a falsely exaggerated magnitude of the RR (due to the incorrect selection of the outcome with the smaller baseline risks) goes beyond the statin therapy that we have addressed in this publication. Similarly to the case presented in which the side effect of a drug is falsely magnified, the beneficial effects of a drug can also be falsely exaggerated; therefore, we believe that not only the RR for the outcome with the higher baseline risks should be reported but also an absolute measurement of association (NNT/NNH) should be reported mandatorily.

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Authors' contribution: LFK and JCS analysed the data and drafted the initial manuscript. SAD conceived the study and all authors critically revised the manuscript for intellectual content.

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TABLES

Table 1: Data extracted from the five RCTs comparing intensive-dose with moderate-dose of statin therapy for no-onset of diabetes

	Intensive dose	**Moderate dose**	**Follow-up**
	No-onset of diabetes/Total, No. (%)		(years)
PROVE IT-TIMI 22 (2004) (17)	1606/1707 (94.083)	1589/1688 (94.135)	2
A to Z (2004) (1)	1703/1768 (96.324)	1689/1736 (97.293)	2
TNT (2005) (3)	3380/3798 (88.994)	3439/3797 (90.572)	5
IDEAL (2005) (2)	3497/3737 (93.578)	3515/3724 (94.388)	4.8
SEARCH (2010) (5)	4773/5398 (88.422)	4812/5399 (89.128)	6.7
Overall	**14959/16408 (91.169)**	**15044/16344 (92.046)**	

Table 2: Meta-analysis of five RCTs comparing intensive-dose with moderate-dose of statin therapy for no-onset of diabetes using the fixed effects model (inverse variance)

	Relative risk (95%CI)	**Risk difference (95%CI)**
PROVE IT-TIMI 22 (2004) (17)	0.99945 (0.98277, 1.01641)	-0.00024 (-0.01189, 0.01140)
A to Z (2004) (1)	0.99004 (0.97821, 1.00201)	-0.00541 (-0.01384, 0.00303)
TNT (2005) (3)	0.98259 (0.96778, 0.99761)	-0.00342 (-0.00997, 0.00314)
IDEAL (2005) (2)	0.99142 (0.98010, 1.00287)	-0.00183 (-0.00697, 0.00331)
SEARCH (2010) (5)	0.99208 (0.97886, 1.00548)	-0.00130 (-0.00630, 0.00370)
Pooled relative risk	**0.99084 (0.98493, 0.99679)**	**-0.00422 (-0.00818, -0.00026)**

NNH 237 (95%CI: NNH 123 – 3847)

Heterogeneity: $\square^2 = 0$

NOTE. The number of events was computed based on the yearly incidence rate and the NNH is reported at 2 years.