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Statins and diabetes: What are the connections?

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Randomized trials suggest moderate-intensity statins increase type 2 diabetes risk by around 11% with a potential further 12% moving to high-intensity statins, such that high intensity may increase risk by 20% or more relative to placebo. These data translate into one extra diabetes case per 100–200 statin recipients over 5 years, with ~10-fold greater benefits on major vascular outcomes. The underlying mechanisms for diabetes harm are not clear but could include modest weight gain (noted in randomized trials), or, speculatively, beta cell harm. Concordant genetic studies link HMG CoA Reductase inhibition to diabetes risk and weight gain. Patients should be warned about a slight diabetes risk when prescribed statin and told that modest lifestyle improvements can i) nullify diabetes risk, and ii) improve cardiovascular risks beyond statins. Doctors should also measure glycemia status post statin commencement, most commonly with HbA1c, and tailor lifestyle advice and care dependent on the results.

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Introduction

In 2001, the Glasgow group reported a hypothesis generating lower 30% risk of incident diabetes with pravastatin compared to placebo in the WOSCOPS trial, a trial of over 6000 men with hypercholesterolemia in the West of Scotland [1]. Moving forwards several years, the JUPITER trial suggested the opposite as more rosuvastatin compared to placebo recipients had a doctor diagnosis of diabetes (n = 270 vs. 216, p = 0.01), even though cardiovascular risk was lowered by 44% with rosuvastatin [2]. Such a

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report generated concern in the cardiovascular community about the glycaemic impact of statins. Our group subsequently collated all the potential randomized trial data we could gather on this topic, collecting unpublished data from several trials such that in 2009 we reported statin recipients across 13 randomized-controlled trials had a 9% (95% CI: 2–17%) higher risk of type 2 diabetes compared to placebo/standard care recipients, with low levels of heterogeneity [3]. We subsequently reported a 12% (4–22%) higher diabetes risk in people randomized to high versus moderate intensity statin across five trials [4]. These two meta-analyses have since been heavily cited and have informed relevant lipid-lowering guidelines and opinion pieces.

In 2015, we repeated the meta-analysis but this time with data from 15 placebo-controlled or standard care control arm trials [5]. The results suggested an overall elevated diabetes risk by 11% (3–20%) in statin relative to placebo/standard control participants (Fig. 1). The highest risk in any trial was seen in the SPARCL trials which tested the impact of atorvastatin 40 mg in elderly subjects post stroke. There was moderate heterogeneity (I^2 = 29.6%) and insufficient power to prove any statin type had a greater impact on diabetes risk. Even so, it did appear that higher intensity statins yielded greater diabetes risks [5].

Notably, trial data on diabetes diagnoses were mostly collected post hoc with heterogeneous methods ranging from a mixture of repeat glycemia testing (fasting glucose) to doctor-diagnosed diabetes. Ongoing individual participant data analysis of statin trials, which has collated more data from all relevant trials as part of the CTT collaboration [6], should help shed more granularity on glycemic impact of statins in both people with and without baseline diabetes, including the time course for glycemia changes.

Numerous other meta-analyses or observational data have since examined this topical subject, but many have important limitations, and none meaningfully extend the results of the three meta-analyses [3–5] co-led by the Glasgow group. In 2018, Collins et al. put these meta-analyses data into context by comparing the number needed to benefit of 10–20 for one less major vascular events with five years of daily high-intensity statin therapy, with the number needed to harm of 100–200 for one new-onset diabetes case, Table 1 [7]. In other words, for every 10 major vascular events prevented, approximately one extra case of diabetes would emerge.

What do the genetics tell us?

Mendelian randomization is a method now familiar to most readers whereby genetic polymorphisms that lead to lifelong differences in one biological pathway can be used to approximate its relevance to long-term risks by comparing outcomes in those with or without such polymorphisms. Such work (for example, using polymorphisms that lower HMG-CoA-Reductase activity, the rate-limited step in cholesterol, synthesis) has been widely used to confirm LDL-c lowering should lower cardiovascular outcomes, but also that longer term statin treatment should yield even greater outcomes benefits than reported in shorter term trials [8]. Using the same polymorphisms, we reported their association with higher diabetes risk, and interestingly also with higher weight in the 2015 meta-analysis [5]. To confirm clinical relevance, we also extracted weight changes from as many trials as we could gather and were able to show statins modestly increased weight (on average 0.24 kg) relative to control arm, with the effect being somewhat greater in the placebo /standard arm control trials (0.33 kg), (Fig. 2) [5]. Interestingly, there was no weight differential in the five low versus high statin intensity trials, which on the face of it seems to go against weight excess explaining the diabetes risk. However, weight is composite of fat and lean mass, and as patients with existing cardiovascular disease (as in low vs high-intensity statin trials) tend to lose weight over time due to unintentional weight loss, any signal of statin-induced fat mass gain could be lost or attenuated.

Other work using genetic analyses and novel Egger regression analyses has suggested that the statin to diabetes effect, in line with the statin to cardiovascular benefit, is likely entirely explainable by the impact of statins on LDL-c levels [9]. In other words, pleiotropic effects are unlikely to explain statin benefits or their actions to worsen glycemia. Of course, the degree of LDL-c reduction is dependent on the degree of reduced activity of HMG CoA Reductase activity, and thus these results are in line with earlier genetic data and with data comparing the impact of high-intensity versus low-intensity statin trial [5]. The one cautionary note with Mendelian randomization genetic studies is that their robustness

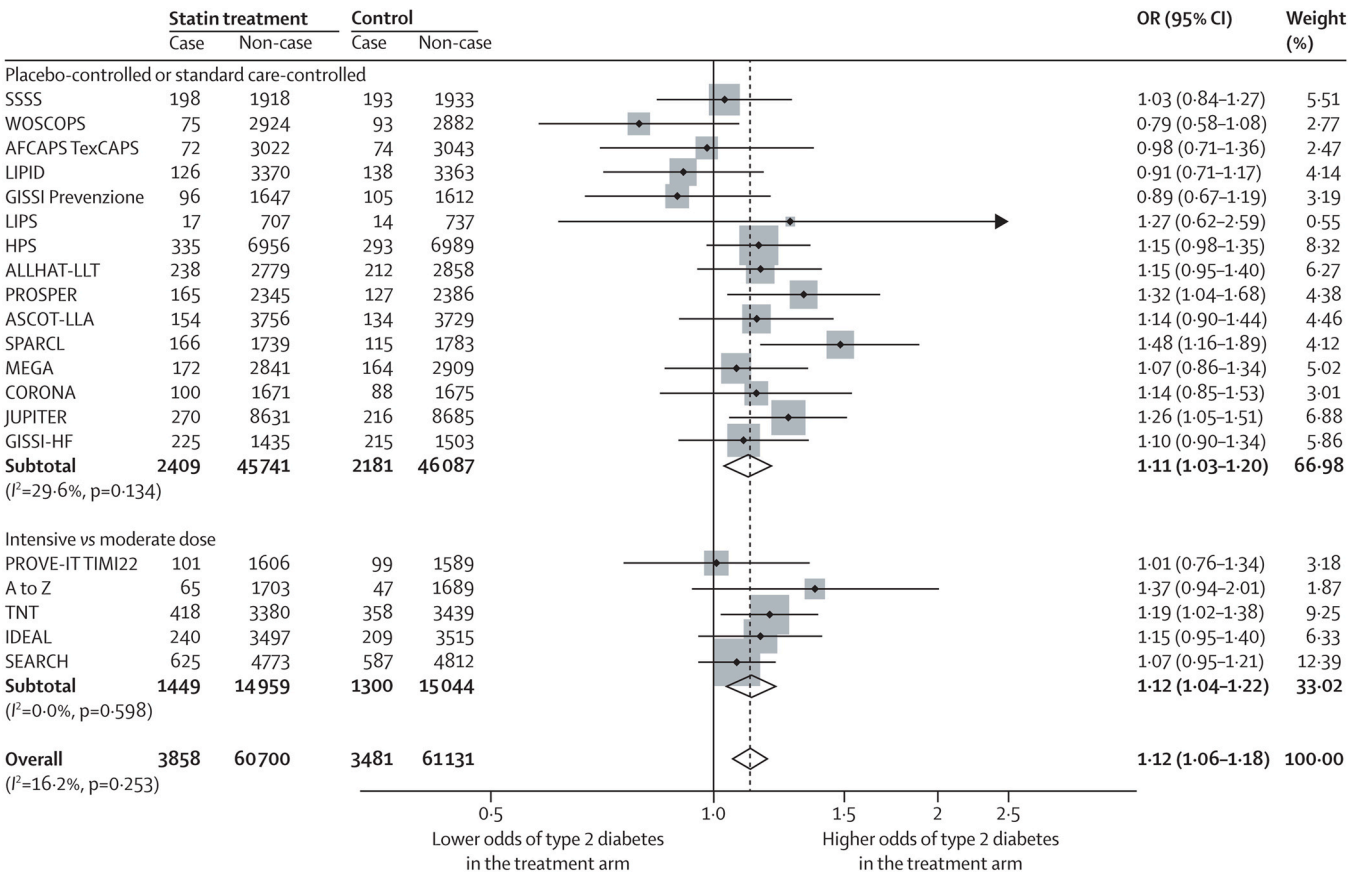

Fig. 1. Effect of statin treatment on new-onset type 2 diabetes. Data were analyzed by random-effects meta-analysis. OR=odds ratio. Case=developed type 2 diabetes. Non-case=did not develop type 2 diabetes. This figure was published in Lancet, Vol No 385, Swerdlow D.I., Preiss D., Kuchenbaecker K.B., et al., HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials, Page Nos 351–361, Copyright Elsevier. (2015). [5].

Table 1
Numbers needed to treat and harm for outcomes associated with five years of daily high-intensity statin therapy.

	Primary prevention		Secondary prevention	
	NNH	NNT	NNH	NNT
Major vascular events		20		10
New diabetes	100–200		100–200	
Hemorrhagic stroke	1000–2000		1000–2000	
Myopathy	2000		2000	

Based on data from Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388(10059):2532–61.

depends on the preciseness of the genetic instrument used; not uncommonly chosen instruments are associated with different biological pathways (pleiotropy), leading to erroneous outcomes. Geneticists have developed new mathematical models to try to account for different types of confounding but, even so, the answers are not always as accurate as headlines would suggest.

Potential impact of other lipid-lowering drugs from genetics and trials

Of the other lipid-lowering drugs which have looked at this question, most robust data come from studies of PCSK9i. Here, genetic studies based on several different polymorphisms suggest a modest impact on diabetes risk and weight gain [10]. However, data from two large outcome trials have looked at this question and do not show appear to show any clear impact on diabetes risk. For example, in FOURIER, adjudicated cases of new-onset diabetes did not differ significantly between the evolocumab or placebo groups (hazard ratio, 1.05; 95% CI, 0.94–1.17) [11], whereas in ODYSEY OUTCOMES trial, 9.6% of alirocumab recipients develop new-onset diabetes versus 10.1% in the placebo group [12]. The one cautionary note was the shorter duration of these trials at 2.2 and 2.8 years, respectively, necessitating continued vigilance in ongoing trials.

Some groups have simultaneously conducted Mendelian randomization studies linking several lipid-lowering targets and their impacts on diabetes. For example, Lotta et al. confirmed links between HMG CoA Reductase genes and diabetes but also reported that genes near NPC1L1, encoding the molecular target of ezetimibe, may be associated with the highest risk of type 2 diabetes of any lipid target. The OR for a genetically predicted 1-mmol/L reduction in LDL-C via this pathway was 2.42 [95% CI, 1.70–3.43] [13]. The same paper also predicted a higher diabetes risk for PCSK9i. However, as noted, there is, as yet, no clear evidence for PCSK9i impact on diabetes risk in major trials [11,12]. Preliminary data also goes against any clear impact of ezetimibe on the glycemic status on top of statins [14]. Analyses from the IMPROVE-IT trial also did not confirm an impact of ezetimibe on diabetes risk (Robert P Giugliano, personal communication). Thus, some caution is required about ezetimibe, which, by its mode of action, would not be predicted to influence diabetes risk.

The one other recently approved agent of interest is Bempedoic acid, which is an oral ATP citrate lyase inhibitor, and a prodrug converted to active coenzyme A form by enzymes found only in the liver and not in muscles. Current accumulated randomized controlled phase 3 trial evidence suggests Bempedoic acid lowers: i) HbA1c levels modestly (by around 0.12–0.06%, in diabetes and pre-diabetes, respectively) and ii) weight by around 0.42 and 0.35 kg relative to placebo in those with diabetes and pre-diabetes, respectively [15]. There was no evidence of weight loss in non-diabetes in those trials. Interesting, preliminary genetic data on ACLY variants also suggest a potential borderline ($p = 0.05$) reduction in the risk of diabetes, data in stark contrast to the opposite findings for HMG CoA Reductase variants) [16].

Table 2 provides a summary of the commonly used LDL-c lowering agents in practice, and their effects on diabetes risks reported variably in genetic studies and clinical trials. To date, only statins have reliable evidence for an adverse impact on diabetes risk, albeit modest in nature. More data on Bempedoic acid will come from the CLEAR Harmony trial due to report in the near future. If this confirms a

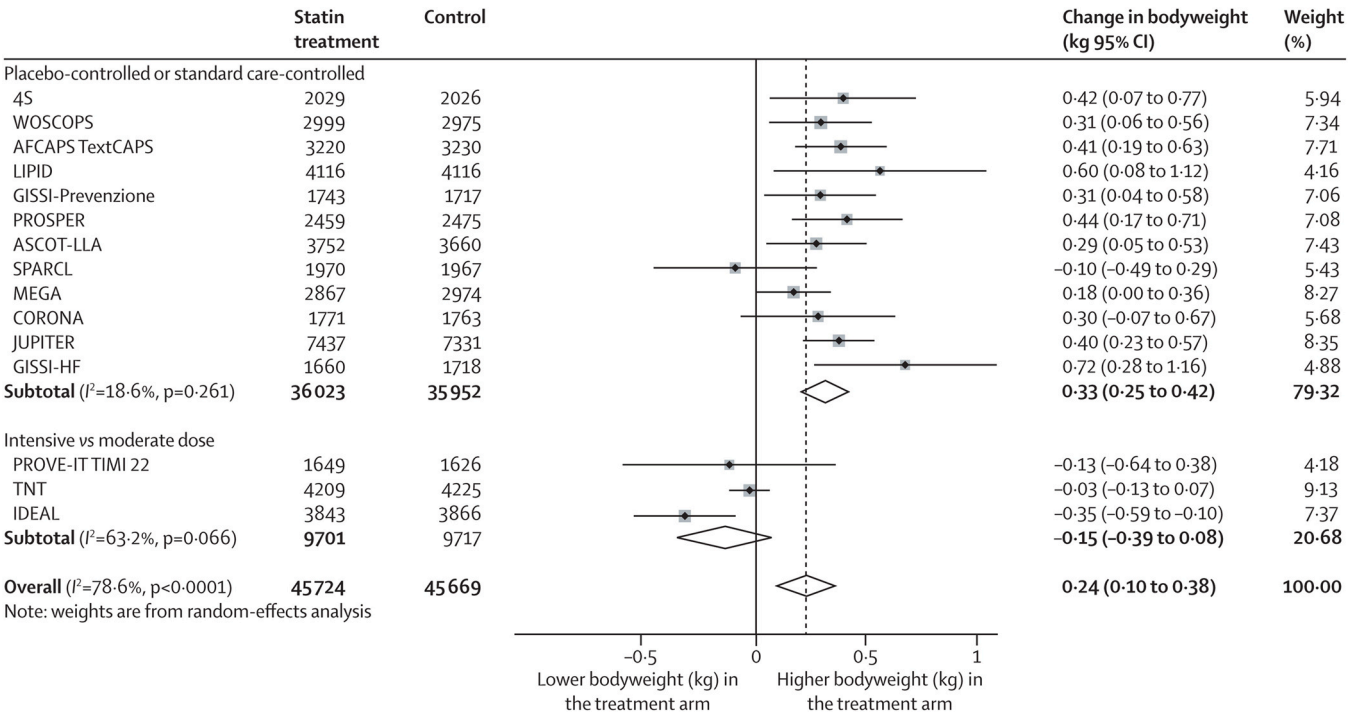

Fig. 2. Effect of statin treatment on body weight. Data were analyzed by random-effects meta-analysis. In most trials, the total number of participants without type 2 diabetes at baseline for whom bodyweight data were available was smaller than the total number for whom data were available for the analysis of new-onset type 2 diabetes. This figure was published in Lancet, Vol No 385, Swerdlow D.I., Preiss D., Kuchenbaecker K.B., et al., HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials, Page Nos 351–361, Copyright Elsevier. (2015). [5].

Table 2
Summary of top-line results on the impact of the four most used lipid-lowering agents on diabetes and weight gain in trials and genetic studies.

Class of lipid-lowering agent	Genetics		Trials		Comment
	DM Risk	Wt Gain	DM Risk	Wt change	
Statins (HMGCoA Reductase)	✓	✓	✓	✓ weight gain	Diabetes and weight effect modest—likely mitigated by lifestyle improvements. More long-term data needed for statins on body composition
Ezetimibe (NPC1L1)	✓	NR	NR	NR	More data on ezetimibe impact on diabetes risk coming later this year but preliminary data from IMPROVE-IT do not support an impact on diabetes risk
PCSK9i	✓	✓	No	No	Two large trials show no clear impact on diabetes risk which suggests the current genetics may not be accurate or that risk will take longer to materialize
Bempedoic acid (ACLY)	✓ but lower (borderline)	NR	✓ Lower risk	✓ Weight reduction	Short-term trials suggest a reduction in HbA1c, but longer-term data needed, and no mechanistic work done as yet. Note urate levels increase with Bempedoic acid.

NR = not recorded.

lower diabetes risk, studies on potential mechanisms for how this class lowers HbA1c whilst increasing urate levels would be useful.

Mechanisms of diabetes risk of statins: largely unknown

There is no clear consensus on the mechanisms by which statins increase diabetes risk. The most convincing pathway for a contributory effect is the statin-induced weight gain given weight excess is a key feature of diabetes pathogenesis. Mendelian randomization data suggest around half of the impact of statins on diabetes risk may be accounted for their impact on weight [17]. However, the trial data showed only a modest increase in weight (~0.66 pounds) relative to placebo/standard control arm, which seems too low to account for a 10–20% higher diabetes risk, unless the statin-induced weight gain is attenuated by a subtle loss of muscle mass. There was a very minor increase in creatine kinase levels by approximately 0.02 times the upper limit of normal with statins in a recent individual participant data meta-analysis of statin randomized trials [18]. To what extent such a small rise in creatine kinase levels reflect changes in muscle mass or function to enhance diabetes risk is uncertain. More studies are needed to tease out the impact of statins on body composition, though such work would need very large numbers to have adequate power.

In terms of insulin resistance, there is some weak and mixed evidence for worsening insulin resistance (based on surrogate markers) with statins but the evidence base in general supporting this conclusion is rather weak, as we have previously summarized [19]. Surprisingly, there is a lack of robust clamp-based randomized trials of sufficient power testing this question. There are also hypothetical arguments to support an adverse impact of statins on beta cell function, potentially arising from an increase in intracellular cholesterol in beta cells, again as previously discussed [19]. However, once again, robust randomized trials are lacking to support or refute these suggestions. Presently, therefore, definitive mechanisms explaining the statin impact on diabetes risk is far from established.

Clinical relevance of the data

Statin treatment has overwhelmingly shown cardiovascular benefit with numbers needed to benefit of 20 and 10 patients treated for five years to prevent one major vascular event in primary and secondary prevention populations, respectively [7]. As noted, these numbers compare with numbers needed to harm of 100–200 for one extra case of diabetes, which should be remembered as a diagnosis of elevated glucose levels, not a hard outcome per se. Such diabetes risks are also, predicably, higher in absolute terms in those with greater risk factors for diabetes given they will be closer to the threshold for diagnosis of diabetes in the first place [20]; of course, such patients are also often at higher-than-average cardiovascular risk. The reverse is also true in that those with no or minimal risk factors for diabetes have low absolute risks of converting to diabetes when on a statin.

Concerns about diabetes risk are therefore seldom a reason to withhold statins, but it should be mentioned to patients even if it is modest, especially as diabetes risk can be mitigated by simple lifestyle changes. Patients should also be told that any modest and ideally sustainable lifestyle changes will also help prevent vascular events beyond statin treatment. In this way, the statin-associated diabetes risk is an important point to get across to patients to help ensure they take lifestyle changes more seriously than they might otherwise. These points should be potentially more carefully mentioned to patients at elevated diabetes risk.

In patients with existing diabetes, the overall HbA1c change with statins is often trivial [21–23] and, currently, of little clinical concern. Again, more relevant data on this point should soon be forthcoming from a re-analysis of data from multiple statin outcome trials. Of course, it should be remembered that even if HbA1c does rise modestly with statins in people with diabetes, it may take many years to impact microvascular risk (if at all), whereas cardiovascular risk would be reduced rapidly.

A final point is that when type 2 diabetes develops in general, many other risk factor changes are evident such as higher blood pressure, higher BMI, and a characteristic dyslipidemia. We know statins increase weight modestly, but there is no evidence to support an impact on blood pressure and, LDL-c improves with statins, as do triglyceride levels. Thus, the impact of statin-induced new-onset diabetes on microvascular risk may not be the same as new-onset diabetes in general but, once again, more data are needed to prove this point.

Summary

Of all the lipid-lowering agents, statins have the best evidence to support a small, but significant impact on the development of new-onset diabetes. Such risks appear higher in relative terms at greater statin intensities and greater in absolute terms when patients have more diabetes risk factors at baseline. However, such patients often have higher average cardiovascular risks. Statins increase glycemia levels very modestly, but the underlying mechanisms remain uncertain. A slight weight gain may be contributory but more research on their impact on body composition, tissue insulin sensitivity, and beta cell function is needed to resolve numerous speculations. Such trials may never be conducted with sufficient power. More data on HbA1c level changes with statins will be shortly available from additional analyses of randomized trials, including how fast HbA1c rises and whether it continues to rise over time and, if and how fast it declines once statins are stopped.

Presently, statin reduction of major vascular outcomes outweighs their impact on diabetes risk; one extra diabetes case occurs per 100–200 statin recipients over 5 years, with benefits on major vascular outcomes being ~10-fold greater, at least at current cardiovascular risk thresholds for statin treatment. Clinically, doctors need to counsel patients about the potential for very modest increase in diabetes risk when commencing statins and advise that by improving lifestyle—walking a little more and eating a better-quality diet—such risks can be mitigated. Patients should also be told that modest lifestyle changes can also help lower cardiovascular risks beyond impact of statins [24]. Doctors should also measure HbA1c or fasting glucose on those recently commenced on statins to diagnose pre-diabetes or new diabetes and treat accordingly or, where appropriate, give patients an opportunity to lower their HbA1c levels meaningfully by extra lifestyle efforts (often involving weight loss) before reassessing glycaemic status.

Practice points

- Counsel about the potential for very modest increase in diabetes risk when commenced on statins and advise that improving lifestyle—by walking a little more and improving diet—will mitigate such risks. Also mention that such modest lifestyle changes can also help lower cardiovascular risks beyond impact of statins and can be enjoyable after a period of perseverance.
- Note that absolute risks of diabetes conversion on a statin will be far greater in those patients with risk factors for diabetes, so that lifestyle changes in such individuals should be strongly recommended.
- Counsel that prevention of cardiovascular events by statins substantially overwhelms any diabetes risk in people considered at high enough risk to be recommended a statin.
- Measure HbA1c or fasting glucose on those recently commenced on statins to diagnose pre-diabetes or new diabetes and treat accordingly or, where appropriate, give chance to lower HbA1c meaningfully by extra lifestyle efforts, and reassess glycaemic status.

Research agenda

- There is a need for a detailed analysis of individual participant data from statin trials to examine impacts of statins on HbA1c levels in people with and without diabetes, as well test for any differences by dose or length of statin treatment. Such data could also inform on how quickly HbA1c rises and whether it continues to rise over time or not.
- More mechanistic studies are needed to examine potential mechanisms by statins increase diabetes risks, including the impact of statins on body composition. More data on mechanisms for potentially lower risk of diabetes with Bempedoic acid may also be informative.
- Careful analyses of ongoing trials targeting LDL-c reduction by differing methods are needed to examine for any effects on diabetes risk. Such trials include CLEAR HARMONY (Bempedoic acid), VESALIUS (evolocumab) or ORION-4 (Inclisiran).
- More work should be done to see if patients take the diabetes risk associated with statins seriously enough to motivate for lifestyle change but, if not, how advice can be better delivered to help them do so.

Conflict of interest statement

NS has consulted for and/or received speaker honoraria from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and received grant support paid to his University from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics outside the submitted work.

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