Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract

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Aims
To objectively appraise evidence for possible adverse effects of long-term statin therapy on glucose homeostasis, cognitive, renal and hepatic function, and risk for haemorrhagic stroke or cataract.

Methods and results
A literature search covering 2000–2017 was performed. The Panel critically appraised the data and agreed by consensus on the categorization of reported adverse effects. Randomized controlled trials (RCTs) and genetic studies show that
statin therapy is associated with a modest increase in the risk of new-onset diabetes mellitus (about one per thousand patient-years), generally defined by laboratory findings (glycated haemoglobin ≥6.5); this risk is significantly higher in the metabolic syndrome or prediabetes. Statin treatment does not adversely affect cognitive function, even at very low levels of low-density lipoprotein cholesterol and is not associated with clinically significant deterioration of renal function, or development of cataract. Transient increases in liver enzymes occur in 0.5–2% of patients taking statins but are not clinically relevant; idiosyncratic liver injury due to statins is very rare and causality difficult to prove. The evidence base does not support an increased risk of haemorrhagic stroke in individuals without cerebrovascular disease; a small increase in risk was suggested by the Stroke Prevention by Aggressive Reduction of Cholesterol Levels study in subjects with prior stroke but has not been confirmed in the substantive evidence base of RCTs, cohort studies and case–control studies.

Conclusion

Long-term statin treatment is remarkably safe with a low risk of clinically relevant adverse effects as defined above; statin-associated muscle symptoms were discussed in a previous Consensus Statement. Importantly, the established cardiovascular benefits of statin therapy far outweigh the risk of adverse effects.

Keywords

Statin • Adverse effects • Glucose homeostasis • Metabolic syndrome • Cognitive function • Renal function • Liver function • Haemorrhagic stroke • Cataract

Introduction

Statins [3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors] are recommended as the treatment of first choice for management of hypercholesterolaemia and combined hyperlipidaemia by European guidelines for cardiovascular disease (CVD) prevention and lipid management. The efficacy of these agents in decreasing low-density lipoprotein cholesterol (LDL-C), a causal factor in the pathophysiology of atherosclerotic cardiovascular disease, and in preventing both first and recurrent cardiovascular events (with or without type 2 diabetes), is indisputable.

Large randomized controlled trials (RCTs) have clearly established the benefit/risk ratio of this treatment. Since several trials are evaluating the effects of a statin-containing polypill on modifiable risk factors, the use of statins is likely to expand into a wider cross-section of the population. Consequently, critical appraisal of evidence relating to possible unintended effects of long-term statin therapy is needed, on the one hand to accurately assess their incidence, and on the other, to place often exaggerated perceptions of side effects among patients, the general public and some healthcare providers, in their correct perspective.

Data from RCTs provide reliable information on the safety of statin therapy, but this information relates to the specific patient populations which fulfilled the inclusion criteria and were treated for a relatively short duration, typically less than 5 years. Less frequent adverse effects of treatment may only emerge after long-term exposure in very large numbers of patients. For example, while single studies were contradictory with respect to the risk of new-onset diabetes mellitus (DM), meta-analyses and large data bases provided clear evidence, especially in susceptible individuals with the risk factor cluster of the metabolic syndrome who may already be in a pre-diabetic state.

It remains to be seen if the pharmacology of different statins (Table 1) is relevant to the issue of statin side effects. Indeed, the metabolism of statins is distinct. For example, genetic differences in the activity of the cytochrome P450 (CYP) system can affect statin interactions with other drugs, whereas genetic differences in membrane transporters can alter first pass hepatic uptake, a major determinant of residual circulating concentrations and ultimately of peripheral tissue exposure. The issues described above highlight the critical need for an objective appraisal of adverse effects attributed to statins in order to differentiate the perception from the reality of the potential risks associated with statin therapy, specifically on glucose homeostasis, and cognitive, renal and hepatic function, as well as the risk for haemorrhagic stroke and cataract. This appraisal will provide important evidence-based information not only for patients, clinicians and the wider spectrum of healthcare professionals, but also for public health policy makers.

Statin-associated muscle symptoms

Statin-associated muscle symptoms (SAMS, the focus of a separate Consensus Statement) are the predominant adverse effect encountered in clinical practice (Figure 1), and impact adherence and ultimately clinical outcomes (Box 1). A much-debated issue is whether SAMS represent real or nocebo effects. A nocebo effect is caused by negative expectations about the effects of treatment, arising from information provided by clinicians and/or the media about possible side effects, which lead to higher reporting rates for adverse effects of the treatment than would otherwise be expected. The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) Study Group addressed this issue by comparing the incidence of four different types of adverse events with statin therapy, including muscle-related symptoms, during both the blinded, placebo-controlled trial and its open-label extension study. They concluded that a nocebo effect may explain the higher incidence of SAMS in observational studies vs. RCTs, although others have noted that the overall rate of muscle-related events decreased from 2.03% in the blinded phase to 1.26% when subjects were aware that they were on a statin. Perhaps the take home message for clinicians is that they should be cautious about prematurely attributing muscle symptoms to statin therapy, without further investigation of their cause.

Search strategy

The literature was searched using Medline, Current Contents, PubMed, and relevant references with the terms ‘statin safety’, ‘statin...
adverse effects', 'statin AND cognitive function', 'statin AND plasma glucose', 'statin AND diabetes', 'statin AND renal function', 'statin AND hepatic function', 'statin AND stroke', 'statin AND peripheral neuropathy', 'statin AND cardiovascular disease', 'statin AND atherosclerosis', 'statin AND atherothrombosis'. Main articles published in English between 2000 and 2017 were included, as well as European guidelines on CVD prevention and lipid management.1,2 This Review was based on discussions at meetings of the EAS Consensus Panel organized and chaired by M.J.C. and H.N.G., where the search results and drafts of the Review were critically and comprehensively appraised. The content of this Review resulted from a consensus of considered opinions and insights of the expert members of the Panel.

**Effects on glucose homeostasis**

Statin therapy is known to be associated with a small increment in fasting blood glucose levels.2 In a meta-analysis of 13 RCTs involving 91,140 subjects without diabetes at baseline, statin treatment increased incident DM by ~9%, representing one additional case of

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**Table I** Comparative pharmacology of statins

|                        | Lovastatin | Simvastatin | Atorvastatin | Pitavastatin | Fluvastatin | Rosuvastatin | Pravastatin |
|------------------------|------------|-------------|--------------|--------------|-------------|--------------|-------------|
| **IC50 HMG-CoA reductase (nM)** | 2–4        | 1–2 (active metabolite) | 1.16         | 0.1          | 3–10        | 0.16         | 4           |
| **Oral absorption (%)**    | 30         | 60–85       | 30           | 80           | 98          | 50           | 35          |
| **Bioavailability (%)**   | 5          | <5          | 12           | 60           | 30          | 20           | 18          |
| **Protein binding (%)**   | >98        | >95         | >98          | 96           | >98         | 90           | 50          |
| **Half-life (h)**         | 2–5        | 2–5         | 7–20         | 10–13        | 1–3         | 20           | 1–3         |
| **Metabolism by CYP450**  | 3A4 (2C8)  | 3A4 (2C8, 2D6) | 3A4 (2C8)   | (2C9)        | 2C9         | 2C9 (2C19)   | (3A4)       |
| **Cellular transporter**  | OATP1B1 (MRP2) | OATP1B1      | OATP1B1 (MRP2) | OATP1B1 | OATP1B1 | OATP1B1 (MRP2) |
| **Daily dose (mg)**       | 10–40      | 10–40       | 10–80        | 1–4          | 80 (retard formulation) | 5–40        | 10–40       |

Adapted from Sirtori.10 Figures in parentheses indicate a minor metabolic pathway or transporter. CYP450, cytochrome P450; IC50, 50% inhibitory concentration; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MRP2, multidrug resistance-associated protein 2; OATP1B1, Organic Anion Transporting Polypeptide 1B1.

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**Figure I** Overview of the relative prevalence of the main types of adverse effects reported with statin therapy. RCT, randomized controlled trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels.
diabetes (12.23 cases with statin vs. 11.25 cases with control) per 1000 patients per year of exposure, but also prevented five first CVD events. This is, however, an underestimate as multiple recurrent events were not considered. Another meta-analysis including ∼40 000 patients with stable coronary heart disease or recent acute coronary syndrome in five RCTs showed that high intensity statin therapy increased the risk of incident DM by 12%, but also reduced the risk of CVD events by 16%, or in absolute terms, prevented 3.5 CVD events for each additional case of diabetes. In this analysis, a ‘case of diabetes’ was defined by serum glycated haemoglobin (HbA1c) >6.5, a laboratory finding that has no immediate impact on quality of life, and therefore should not be compared with outcomes such as stroke or death from myocardial infarction. The risk of incident DM with statin treatment increases with an increasing number of components of the metabolic syndrome, as shown by post hoc analyses of the justification for the use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), Treating to New Targets (TNT), Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL), and Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trials, especially in individuals with the highest fasting blood glucose levels at initiation of statin therapy; this effect may be substantially higher in physically active, and exhibited lower levels of high-density lipoprotein cholesterol (HDL-C) and higher triglycerides, fasting blood glucose, and HbA1c.22 To put these findings in context, the rate of CVD events for each additional case of diabetes.18 In this analysis, a ‘case of diabetes’ was defined by serum glycated haemoglobin (HbA1c) >6.5, a laboratory finding that has no immediate impact on quality of life, and therefore should not be compared with outcomes such as stroke or death from myocardial infarction. 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In the Metabolic Syndrome in Men (METSIM) cohort in 8749 men (2142 on a statin) aged 45–73 years with features of the metabolic syndrome but without a diabetes diagnosis, intense statin treatment was associated with a 46% increase in incident DM (11.2% vs. 5.8% in those not on a statin, P < 0.001) over 5.9 years follow-up, representing 10 new cases per 1000 patients per year of exposure. These individuals were older, more obese, less physically active, and exhibited lower levels of high-density lipoprotein cholesterol (HDL-C) and higher triglycerides, fasting blood glucose and HbA1c. To put these findings in context, the rate of conversion to DM in subjects with confirmed impaired glucose tolerance not on a statin was 110 per 1000 subjects per year of exposure in the Diabetes Prevention Program, and 200 per 1000 Japanese participants per year of exposure in the J-PREDICT trial (Odawara M, Late Breaking Studies, American Diabetes Association Congress, 2013). Among such high risk patients who developed new-onset DM, the risk of CVD events was lower on statin therapy supporting the notion that, at least within the time scale of these trials, potential adverse effects of hyperglycaemia do not negate the benefits of LDL-C reduction. Furthermore, observational data show that patients who developed DM while receiving a statin not only had a lower rate of macrovascular disease but also microvascular disease complications normally linked to diabetes. Thus, the net benefit among high risk patients in need of statins favours their use, consistent with the Joint Task Force guidelines recommendations. These data are consistent with findings among patients with DM treated with statins who derive a similar relative risk (RR) reduction per unit reduction in LDL-C but a greater absolute benefit. Determining whether the effect of statins on DM risk is an on-target (i.e. inhibition of HMG-CoA reductase) or off-target action will help in understanding whether the effect of a statin on glucose metabolism is a drug or drug class effect. Mechanistically, statins could increase blood glucose by increasing insulin resistance, possibly mediated by changes in circulating free fatty acids, impairing beta-cell function, or alternative mechanisms, or a combination of these. Indeed, a meta-analysis of new-onset DM and weight change data from up to 20 major RCTs (n = 129 170) also showed that patients who received a statin gained on average 0.24 kg compared with control at study close. This overall question was clarified by a Mendelian randomization study in ~200 000 individuals, in which the associations between common genetic variants (rs17238404 and rs12916) of the HMGCR gene, the target of statins, and body weight, body mass index (BMI), waist circumference, plasma insulin and glucose, and DM risk were evaluated. These two variants were not only associated with lower LDL-C at a genome wide level of significance, but also a small increase in the risk of DM, and higher blood glucose, insulin levels, body weight, waist circumference and BMI (Table 2). These meta-analyses of genome-wide association studies of BMI and plasma insulin revealed directionally concordant associations of the same variants (or suitable proxies) with both these traits, although associations of both variants with fasting insulin were not statistically significant after adjustment for BMI. Long-term follow-up from the METSIM cohort showed that the increased DM risk with statin therapy was attributable to decreases in insulin sensitivity and insulin secretion, although recent reports associated the gut microbiota and the metabolic profile with these metabolic traits, as well as the effects of statin treatment on such traits. Alternatively, this effect on glucose homeostasis may be a class effect of statins mediated via LDL. Three large genetic studies which assessed life-long exposure to lower LDL-C levels due to carriage of genetic variants of other LDL-lowering drug targets, namely PCSK9 and NPC1L1 showed an increased risk of DM but only

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**Box 1 Key points about SAMS for clinicians**

- **What are SAMS?** Muscle pain, weakness and aches, usually symmetrical and proximal, affecting the thighs, buttocks, calves and back muscles. Not normally associated with marked creatine kinase (CK) elevation.
- **When do SAMS occur?** Tend to occur early (within 4–6 weeks of starting a statin), after an increase in statin dose, or with initiation of an interacting drug.
- **Who is at risk of SAMS?** The very elderly (>80 years), notably female, or with low body mass index or of Asian descent, with a history of muscle disorders, or concurrent conditions (e.g. acute infection, impaired renal or hepatic function, diabetes, HIV) or concomitant interacting medications.
- **How did the EAS Consensus Panel define SAMS?** By the nature of muscle symptoms, and their temporal association with statin initiation, discontinuation, and response to repetitive statin re-challenge.
- **What determines management of SAMS?** The magnitude of CK elevation, and the patient’s global cardiovascular risk.
in those individuals with impaired glucose tolerance. Whilst this predicted increased risk has not been observed so far at very low LDL-C levels attained with add-on treatment with a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor,37,38 or ezetimibe,39 prolonged drug exposure particularly among those more at risk of developing diabetes may be required to observe an effect. It is also noteworthy that a reduced incidence of diabetes has been observed in individuals with causative LDLR mutations for familial hypercholesterolaemia.40 On the other hand, causative APOB mutations for familial hypercholesterolaemia were not associated with diabetes.41 Clearly, the relationship of circulating LDL to predisposition to diabetes is unresolved, as highlighted by the Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial with the cholesteryl ester transfer protein inhibitor, anacetrapib, in which a lower risk of diabetes was observed despite an additional 17% reduction in LDL-C on top of background statin treatment with ~100 000 person years of exposure.42

Thus, evidence suggests that statins affect glucose homeostasis and are associated with a small risk of incident DM. Caution is needed, however, as studies have generally not included glucose tolerance testing, the gold standard for the diagnosis of diabetes, before and after statin treatment. Moreover, while this effect has been thought to be a drug class effect, recent insights suggest that this may not be the case.43–45 Both pravastatin and pitavastatin have been recognized as neutral for effects on glycaemic parameters in patients with and without DM, as reflected by regulatory labelling.46,47 In the absence of head-to-head studies, definitive statements as to whether any of the statins differ in their effect on glycaemia are not possible.

Take home messages

- Concordant evidence from RCTs and genetic studies indicate that statin treatment is associated with a modest increase in the risk of new-onset DM of approximately one case per 1000 patients per year of exposure but also prevents five new CVD events.
- People with features of the metabolic syndrome or prediabetes are at significantly greater risk of this adverse effect, although conversion to DM without statin is also higher.
- In most studies diagnosis of ‘DM’ was based on a laboratory finding of an HbA1c >6.5 without symptoms; the relevance of this HbA1c based conversion to diabetes for long-term morbidity and mortality will require long-term follow-up.
- Patients should be reassured that the benefits of statins in preventing CVD events far outweigh the potential risk from elevation in plasma glucose, especially in individuals with increased HbA1c.

Cognitive function

Whether statin treatment has a possible effect on cognitive function is an important issue, especially with the pandemic of dyslipidaemia associated with diabetes and insulin resistance on the one hand, and changing demographic patterns affecting the prevalence of dementia on the other. Epidemiological studies have documented an association between high cholesterol levels and increased risk of
| Year of citations | Description of studies                                                                 | Results                                                                                     | Conclusion                                                                 |
|-------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 2010<sup>10</sup> | Genome wide association study (GWAS) of genetic variants for BMI (n = 249 796)         | • Showed directionally concordant associations of HMGCR variants (or suitable proxies) with BMI | The effect of statins on diabetes risk is at least partly explained by an on-target effect on body weight/BMI |
| 2012<sup>11</sup> | GWAS of genetic variants for insulin (n = 133 010)                                      | • Showed directionally concordant associations of HMGCR variants (or suitable proxies) with fasting insulin; this was abrogated after adjustment for BMI |                                                                      |
| 2015<sup>19</sup> | Mendelian randomization study (n ~200 000 subjects) of common HMGCR gene variants     | Each allele of the HMGCR gene variant rs17238484G was associated with significant increases in |                                                                      |
|                  |                                                                                       | • Plasma insulin (1.62%, 95 CI 0.53–2.72)                                                   |                                                                      |
|                  |                                                                                       | • Plasma glucose (0.23%, 95 CI 0.02–0.44)                                                   |                                                                      |
|                  |                                                                                       | • Body weight (kg) (0.30, 95% CI 0.18–0.43)                                                |                                                                      |
|                  |                                                                                       | • BMI (kg/m<sup>2</sup>) (0.11, 95% CI 0.07–0.14)                                         |                                                                      |
|                  |                                                                                       | • Waist circumference (cm) (0.32, 95% CI 0.16–0.47)                                       |                                                                      |
|                  |                                                                                       | • Waist–hip ratio (0.001, 95% CI 0.0003–0.002)                                             |                                                                      |
|                  |                                                                                       | The other HMGCR variant (rs12916) showed concordance with these findings                   |                                                                      |
| 2015<sup>19</sup> | Meta-analysis of 20 RCTs (n = 129 170)                                                 | Statin users gained on average 0.24 kg compared with control at study close                 | The effect of statins on diabetes risk may be mediated by an effect of LDL on beta- cell function |
| 2016<sup>12</sup> | Mendelian randomization study using genetic risk scores for variants in HMGCR and PCSK9 genes associated with lower LDL-C levels (n = 112 722) | Variants in HMGCR and PCSK9 genes associated with lower LDL-C levels were also associated with 11–13% increase in diabetes risk per 10 mg/dL decrease in LDL-C |                                                                      |
| 2016<sup>13</sup> | Meta-analyses of genetic association studies for LDL-lowering alleles in or near NPC1L1, HMGCR, PCSK9, ABCG5/G8, LDLR involving 50 775 individuals with T2DM and 270 269 controls | NPC1L1 variants associated with lower LDL-C levels were directly associated with T2DM risk (odds ratio 2.42, 95% CI 1.70–3.43 per 1 mmoL/L lower LDL-C) |                                                                      |
|                  |                                                                                       | PCSK9 variants associated with lower LDL-C levels were also associated with up to 19% higher T2DM risk per 1 mmoL/L lower LDL-C |                                                                      |
|                  |                                                                                       | HMGCR variants were also associated with T2DM risk                                         |                                                                      |
| 2017<sup>14</sup> | Mendelian randomization study of PCSK9 variants associated with lower LDL-C levels (n = >550 000) | Combined analyses of four PCSK9 variants showed associations with increased fasting glucose (0.09 mmoL/L, 95% CI 0.02–0.15), bodyweight (1.03 kg, 95% CI 0.24–1.82), waist-to-hip ratio (0.006, 95% CI 0.003–0.010), and an odds ratio for T2DM of 1.29 (95% CI 1.11–1.50) per 1 mmoL/L lower LDL-C |                                                                      |
|                  |                                                                                       | There were no associations with HbA1c, fasting insulin and BMI                               |                                                                      |

BMI, body mass index; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.
Table 3  Summary of evidence evaluating possible effects of statins on cognitive function

| Year of citations | Description of studies                                                                 | Results                                                                                                                                                                                                                   | Conclusion                                                                                                                                  |
|-------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 201353            | Meta-analysis of eight prospective cohort studies (n = 57 020 and 2851 cases of dementia) | • Statin use was associated with a lower risk of dementia (relative risk 0.62, 95% CI 0.43–0.81)                                                                                                                    | Statin use was associated with reduction in the risk of dementia                                                                              |
|                   |                                                                                       | Among statin users, there was:                                                                                                  |                                                                                                                                               |
|                   |                                                                                       | • No increased incidence of Alzheimer’s dementia and no difference in cognitive performance related to procedural memory, attention, or motor speed |
|                   |                                                                                       | • No increased incidence of dementia or mild cognitive impairment, or any change in cognitive performance related to global cognitive performance scores, executive function, declarative memory, processing speed, or visual perception |
|                   |                                                                                       | • FDA post-marketing surveillance database review revealed similar rates of cognition-related adverse events as compared to other cardiovascular medications | Published data do not suggest an adverse effect of statins on cognition                                                                         |
| 201354,55         | Systematic review of RCTs and cohort, case–control, and cross-sectional studies and FDA post surveillance marketing database |                                                                                                                                                                                                                      | Published data do not suggest an adverse effect of statins on cognition                                                                         |
|                   |                                                                                       | • There were no significant changes in the Alzheimer’s Disease Assessment Scale-cognitive subscale (P = 0.51) and Mini Mental State Examination (P = 0.10) |                                                                                                                                               |
|                   |                                                                                       | • There was no significant increase in adverse events between statins and placebo (odds ratio 1.09, 95% CI 0.58–2.06)                                                                                                    | Statin therapy does not delay deterioration of cognitive function in patients with dementia                                                   |
| 201456            | Cochrane review of 4 RCTs (n = 1154 with probable or possible dementia)                | • Adverse cognitive outcomes with statin use were rarely reported in trials involving cognitively normal or impaired subjects                                                                                           | Statin therapy is not associated with cognitive impairment                                                                                  |
|                   |                                                                                       | • Cognitive test data failed to show significant adverse effects of statins on all tests of cognition in either cognitively normal subjects (P = 0.42) or Alzheimer’s dementia subjects (P = 0.38) |                                                                                                                                               |
| 201557            | Meta-analysis of 25 RCTs (n = 46 836); 23 RCTs included cognitive testing (n = 29 012) | • In IMPROVE-IT, the incidence of neurocognitive adverse events did not increase at very low LDL-C levels (<0.78 mmol/L or <30 mg/dL)                                                                             | Very low LDL-C levels do not adversely affect cognitive function                                                                             |
|                   |                                                                                       | • In FOURIER, the incidence of neurocognitive adverse events did not increase at very low LDL-C levels (<0.50 mmol/L or <20 mg/dL)                                                                                 |                                                                                                                                               |
| 201739,58         | IMPROVE-IT (n = 15 281)59                                                            | • Over a median 19 months follow-up, there were no significant differences between evolocumab and placebo (statin alone) in the change from baseline in the spatial working memory strategy index of executive function (primary end point), or working memory, episodic memory or psychomotor speed (secondary endpoints) | Low LDL-C levels were not associated with adverse effects on cognitive function as assessed prospectively over 19 months                           |
| 201759            | EBBINGHAUS; prospective nested cohort study of the FOURIER study (n = 1204). Cognitive function was assessed prospectively using the Cambridge Neuropsychological Test Automated Battery | • Over a median 19 months follow-up, there were no significant differences between evolocumab and placebo (statin alone) in the change from baseline in the spatial working memory strategy index of executive function (primary end point), or working memory, episodic memory or psychomotor speed (secondary endpoints) | Low LDL-C levels were not associated with adverse effects on cognitive function as assessed prospectively over 19 months                           |

Continued
Adverse effects of statin therapy

In a review of published literature, the Food and Drug Administration (FDA) concluded that there was no evidence that statins increase the incidence of dementia, mild cognitive impairment, or decline in cognitive performance.54 Despite this, the labelling for statins was amended to include cognitive side effects such as memory loss and confusion, although the FDA emphasized that the cardiovascular benefits of statins outweighed these possible effects.54 Similar conclusions were reported in an updated review.55 These findings are supported by data from prospective studies. The Heart Protection Study used the Telephone Interview for Cognitive Status at final follow-up to assess cognitive performance, and showed no differences between simvastatin and placebo groups for the proportion of patients classified as cognitively impaired, either overall or by baseline age subgroups.65 Additionally, in the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study, which assessed cognitive function at six different time points during the study using four neuropsychological performance tests, there was no difference in cognitive decline between pravastatin and placebo groups over a mean follow-up of 42 months.66

Alzheimer’s disease,48,49 leading some to suggest that improved vascular function with statin treatment could be beneficial in the context of several pathologies that cause dementia.50 On the other hand, it has been suggested that reduction in cholesterol levels with statin therapy may be potentially detrimental for cognitive function.51 Yet the view that statins directly affect the brain is simplistic, given the brain-blood barrier and the fact that the brain is largely self-sufficient with respect to endogenous cholesterol synthesis.52

The variable quality of data pertaining to this question is also problematic. Most clinical trials rely on patient self-report of neurological symptoms such as memory impairment, but have not incorporated rigorous objective testing for cognitive function. Furthermore, the study populations were at low risk for cognitive decline and the study duration may not have been sufficient to observe a cognitive effect. In the post-marketing setting, case reports and observational studies predominate (Table 3).39,53–60 Additionally, whether factors present in midlife that are known to be associated with impaired physical function in the longer-term, equally impact cognitive function is often overlooked.61–64

### Table 3

| Year of citations | Description of studies | Results | Conclusion |
|-------------------|------------------------|---------|------------|
| 201760 | Mendelian randomization studies: | | |
| (1) | 111 194 individuals from the Copenhagen General Population Study and Copenhagen City Heart Study | | |
| (2) | The International Genomics of Alzheimer’s Project (n = 17 008 Alzheimer’s disease cases and 37 154 controls) | | |
| | Low LDL-C levels due to PCSK9 and HMGCR variants mimicking PCSK9 inhibitor and statin treatment had no causal effect on the risk of Alzheimer’s disease, vascular dementia, any dementia, or Parkinson’s disease | | |

CI, confidence interval; EBBINGHAUS, Evaluating PCSK9 Binding antiBody Influence on coGnitive HeAlth in high cardiovascUlar risk Subjects; FDA, Food and Drug Administration; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; IMPROVE-IT Examining Outcomes in Subjects With Acute Coronary Syndrome. Vytorin (Ezetimibe/Simvastatin) vs Simvastatin; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial.
Subsequent analyses have also addressed this question. Prospective observational data analysis (>57,000 subjects followed for a median of 4 years) showed that statin use was associated with a lower risk of dementia [RR 0.62, 95% confidence interval (CI) 0.43–0.81; P = 0.001]. A meta-analysis of more than 46,000 patients in 25 RCTs (23 with cognitive testing), did not identify any significant negative effect of statins on cognitive function, both for cognitively normal subjects or those with Alzheimer’s disease.67 Added to this, a Cochrane review of four trials including 1154 patients with probable or possible Alzheimer’s disease found no significant differences in the Alzheimer’s Disease Assessment Scale—cognitive subscale and the Minimal Mental State Examination between patients treated with statin or placebo,56 implying that statins do not delay cognitive deterioration in patients with known dementia. While transient global amnesia has been linked with statin use in case reports,68 there is no evidence to support causality from the totality of evidence to date.

Another question is whether there is any risk of adverse effects on cognitive function with the very low LDL-C levels attained with the combination of a statin and ezetimibe or a PCSK9 inhibitor. A prespecified analysis of the [Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs. Simvastatin] IMPROVE-IT trial showed no increase in neurocognitive adverse events with ezetimibe compared with placebo when associated with exposure to LDL-C levels <0.78 mmol/L (<30 mg/dL) for up to 6 years.39 Data from the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER) trial involving treatment with evolocumab for up to 4 years, and a pooled analysis of studies of alirocumab treatment for up to 2 years, add further support.68,69 Even at the very low LDL-C levels (<0.5 mmol/L or <20 mg/dL) attained with evolocumab plus moderate or high intensity statin therapy in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, there was no increase in neurocognitive adverse events compared with placebo (statin alone).58

The Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in high cardiovascUlar risk subjects (EBBININGHAUS) study59 assessed the effect of very low LDL-C levels on cognitive function in a subset of 1204 patients who were enrolled in the FOURIER trial over a mean follow-up of 1.8 years. This study used the Cambridge Neuropsychological Test Automated Battery (CANTAB, http://www.cambridgecognition.com), a computerized assessment tool that is specifically designed to assess cognitive function across a range of domains, including episodic and working memory, executive function, psychomotor speed, and attention. Assessment is independent of nuances in language and culture, and therefore suitable for application in large multinational clinical studies. Even at very low LDL-C levels [interquartile range 0.28–0.44 mmol/L (11–17 mg/dL) for the lowest LDL-C subgroup] attained with the addition of evolocumab to moderate to high intensity statin therapy in some patients in the FOURIER trial, there was no change in cognitive function over the trial. Indeed, as reported by the authors, the changes seen over time in each group were an order of magnitude less than the changes found in patients with mild cognitive impairment preceding dementia.70 Finally, in a Mendelian randomization study involving 111,194 individuals from the Danish general population, the Copenhagen General Population Study and the Copenhagen City Heart Study, low LDL-C levels associated with PCSK9 and HMGCR variants had no causal effect on the risk of Alzheimer’s disease, vascular dementia, any dementia, or Parkinson’s disease (Table 3).60 Summary level data from the International Genomics of Alzheimer’s Project on risk of Alzheimer’s disease for variants of PCSK9, HMGCR, or other variants associated with LDL-C lowering supported the same conclusion.60

**Take home messages**
- Statin treatment does not adversely affect cognitive function.
- At very low LDL-C levels attained with the combination of statin plus ezetimibe or a PCSK9 inhibitor, there was no signal for any adverse effect on cognitive function.
- Mendelian randomization analyses support the finding that low LDL-C levels, due to PCSK9 and HMGCR variants mimicking PCSK9 inhibitors and statins, had no causal effect on the risk of Alzheimer’s disease, vascular dementia, any dementia, or Parkinson’s disease.

**Effects on renal function**

With the exception of the hydrophilic statins pravastatin and rosuvastatin, statins are metabolized by the liver and cleared minimally by the kidney. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline has provided recommendations for lipid management in chronic kidney disease (CKD).71 Dose reduction based on estimated glomerular filtration rate may be prudent in patients with severe kidney dysfunction who are receiving intensive statin regimens.71 While few studies have been performed in CKD patients, recent meta-analyses indicate that statin treatment reduces CVD risk in patients with CKD, especially those with mild kidney disease.72–75 There was, however, no clear benefit in patients on dialysis.76–78 Given that statins reduce CVD events by 20% in CKD,79 this has prompted guidelines to recommend statin therapy in CKD patients except those on dialysis.71,72 Mild proteinuria, often transient, is seen at low frequency with high dose statin treatment but is not associated with impaired renal function (as reviewed previously).80,81 This may be caused by reduced tubular reabsorption of albumin, related to inhibition of HMG-CoA reductase and reduced prenylation of proteins involved in endocytosis.82,83 A potential concern, however, is whether high dose statin therapy increases the risk of acute kidney disease.84–86 One retrospective analysis involving more than two million statin users (59,636 with CKD) newly treated with a statin between 1997 and 2008, reported a 34% higher RR of acute renal injury within 120 days of initiation of high vs. moderate intensity statin treatment, although this was attenuated with prolonged statin exposure. This was not seen in patients with CKD.84 While this retrospective analysis may raise concerns, data from RCTs have not shown any increase in risk. A meta-analysis of 24 RCTs involving 15,000 patient years exposure reported no change in the risk of acute renal impairment, and no increase in serious adverse renal events during statin treatment.85 Furthermore, in a number of meta-analyses that have focused on CKD patients, there was no increase in progression of CKD or acute renal events on statin therapy.75,88,89 Indeed, it has been suggested that statins...
may have potential renoprotective effects, or even slow progression of CKD, although no such benefit on renal function was evident in other studies.

**Take home messages**

- Statin treatment is not associated with clinically significant deterioration of renal function.
- Dose reduction based on estimated glomerular filtration rate may be prudent in patients with severe kidney dysfunction who are receiving intensive statin regimens.
- A protective effect of statins on the kidney cannot be excluded but further study is merited.

**Effects on hepatic function**

It is difficult to determine the role of statins in the extremely rare cases of severe liver injury associated with statins. Drug-induced liver injury (DILI) is the most frequent cause of acute liver failure and the need for liver transplantation in Western countries. The most common biomarkers for DILI are alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), serum total bilirubin and alkaline phosphatase (ALP). Hepatocellular injury is generally detected by elevations in serum ALT or AST, elevated ALP marks injury to cells in the bile excretory ducts, and elevated serum total or conjugated bilirubin is indicative of reduced excretory function of the liver. In most cases, DILI is rare, idiosyncratic and unpredictable. Moreover, estimating the frequency of DILI is challenging due to potential genetic, epigenetic, environmental and clinical factors that may confound accurate diagnosis. Liver-mediated drug metabolism and transport have also been implicated in mechanisms underlying DILI. These interacting factors plus the rarity of severe liver toxicity associated with statins, contribute to the difficulty in assessing the role of statins in DILI.

**Elevation in liver enzymes**

Mild elevation in liver transaminases occurs in 0.5–2.0% of patients on any statin, usually within 3 months of initiation of therapy. This may not differ significantly from placebo, and in isolation, is unlikely to be clinically relevant. A systematic meta-analysis of 135 RCTs involving more than 246 000 patients reported that statins as a class produced a 50% higher risk of transaminase elevation compared with control or placebo. There was a clear dose–response relationship for atorvastatin, lovastatin, and simvastatin. These elevations were transient, and usually normalized with continuing therapy. Clinically relevant ALT elevations are rare. An analysis of 49 trials involving more than 14 000 patients, reported persistent elevations in hepatic transaminases (>3 upper limit of normal (ULN)) in 0.1%, 0.6%, and 0.2% of patients on atorvastatin 10 mg, atorvastatin 80 mg, and placebo (Table 4). In patients with mild ALT elevation due to steatosis or non-alcoholic fatty liver disease, statin therapy does not result in worsening of liver disease, although caution may be needed in patients with pre-existing primary biliary cirrhosis. Moreover, the cardiovascular benefits of statin therapy are likely to outweigh any potential safety issues, as highlighted by the Joint Task Force guidelines. Indeed, an updated meta-analysis in more than 120 000 patients with chronic liver disease showed that statin use...
was associated with a lower risk of hepatic decompensation and mortality, and possibly reduced portal hypertension.\textsuperscript{109} Statins should not be prescribed, however, in patients with active hepatitis B virus infection until serum levels of AST, ALT, GGT, total bilirubin, and ALP have normalized.\textsuperscript{110}

Drug-induced liver injury

Idiosyncratic liver injury associated with statins is rare but can be severe. Previous studies of drug-related adverse events have suggested that statins may be implicated in 1–3% of all DILI.\textsuperscript{104,105,111,112} In a real-world setting using the United Kingdom General Practice Research Database (1997–2006),\textsuperscript{105} moderate to severe hepatotoxicity (bilirubin >60 μmol/L, AST or ALT >200 U/L, or ALP >1200 U/L) was reported in 0.09% (71/76 411) patients on atorvastatin vs. 0.06% (101/164 407) on simvastatin (hazard ratio for atorvastatin 1.9, 95% CI 1.4–2.6; \( P < 0.001 \)). Reporting rates were higher at higher doses (40–80 mg/day) (0.44% on atorvastatin and 0.09% on simvastatin).\textsuperscript{105} Data from the Swedish Adverse Drug Reactions Advisory Committee (1998–2010),\textsuperscript{104} reported that 1.2 per 100 000 patients had DILI (defined as transaminase elevation >5 × ULN and/or ALP elevation >2 × ULN) on statin therapy. A similar pattern of liver injury was produced on re-exposure after recovery. Despite increasing statin prescription since the late 1990s, however, the FDA Adverse Event Reporting System database did not identify any increase in the rates of fatal or severe liver injury cases caused by statin use.\textsuperscript{97} Reports of statin-associated serious liver injury were extremely low (<2 per one million patient-years). There were 75 reports of severe liver injury, including requirement for liver transplant \(( n = 11 )\) or death \(( n = 37 )\), of which 30 (14 deaths,

### Table 4 Summary of evidence for possible adverse effects of statin treatment on hepatic function

| Year of citations | Description of studies | Results | Conclusion |
|-------------------|------------------------|---------|------------|
| 2006\textsuperscript{103} | Retrospective pooled analysis of 49 trials \(( n = 14 236 )\); patients were treated with atorvastatin (10 mg or 80 mg) or placebo | • 0.1%, 0.6%, and 0.2% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups had clinically relevant ALT elevation \(( >3 \times \text{ULN on two occasions} )\) | Clinically relevant transaminase elevation with statin therapy is rare; higher doses are associated with a higher risk of transaminase elevation |
| 2013\textsuperscript{102} | Network meta-analysis of 135 RCTs \(( n = 246 955 )\) | • Statin treatment was associated with ~50% higher risk of transaminase elevation \(( \text{odds ratio } 1.51, 95\% \text{ CI } 1.24–1.84 )\) compared with control; however, the frequency of clinically significant transaminase elevation associated with statin therapy was low • Higher doses of statins were associated with higher odds of transaminase elevation | |
| 2009\textsuperscript{104} | Swedish Adverse Drug Reactions Advisory Committee (1998–2010) | Only cases with transaminase elevation >5 × ULN and/or ALP elevation >2 × ULN were included • Statin-induced liver injury was reported for 1.2 per 100 000 patients • Re-exposure to statin can produce the same response | Statin-induced liver injury is very rare |
| 2016\textsuperscript{105} | UK General Practice Database (1997-2006) | Evaluated data for patients with a first prescription for simvastatin or atorvastatin with no prior liver disease, alcohol-related diagnosis, or liver dysfunction. Moderate to severe liver toxicity was defined as bilirubin >60 μmol/L, transaminase >200 U/L or ALP >1200 U/L • Statin-induced liver injury is rare but higher with atorvastatin than simvastatin (0.09% vs. 0.06%, hazard ratio 1.9, 95% CI 1.4–2.6, \( P < 0.001 \)) • Reporting rates were higher at higher doses of each statin | |
| 2011\textsuperscript{97} | FDA Adverse Drug Event Reporting System database | Reporting rates for severe statin-induced liver injury were very low \(( \leq 2 \text{ per million patient-years} )\) • There were 75 reports of severe liver injury; none were highly likely or definitely related to statin therapy | |

ALP, alkaline phosphatase; LT, alanine aminotransferase; CI, confidence interval; FDA, Food and Drugs Administration; RCT, randomized controlled trial; ULN, upper limit of the normal range.
7 liver transplantsations, and 9 cases of severe liver injury) were assessed as possibly or probably associated with statin therapy. No cases were assessed as highly likely or definitely associated with statin therapy (Table 4).112 A recent update from the US National Lipid Association’s Statin Liver Safety Task Force concluded that recorded hepatotoxicity due to statins remains a very rare event.113

Clinically apparent liver injury is likely to be a class effect of statins occurring any time after initiation of statin treatment.114,115 Autoimmune hepatitis is perhaps the most common phenotype for DILI of statin-induced hepatotoxicity. Statins may trigger idiopathic inflammatory myositis or immune-mediated necrotizing myopathy,116 with antibodies against HMG-CoA reductase. Similar mechanisms could contribute to a statin-associated autoimmune hepatitis.

Monitoring liver enzyme elevation
Routine periodic monitoring of liver enzymes during statin therapy is not supported by current evidence, and is thus not recommended in asymptomatic patients.117,118 Indeed, routine periodic monitoring could identify patients with isolated increased ALT, AST, or GGT levels, and prompt physicians to reduce or discontinue statin therapy, thereby placing patients at increased risk for CVD events. It is, however, reasonable to measure hepatic function if symptoms suggestive of hepatotoxicity arise (e.g. unusual fatigue or weakness, loss of appetite, abdominal pain, dark-coloured urine, or yellowing of the skin or sclera). If the patient develops ALT levels >3× ULN (or lower when combined with a new increase in bilirubin levels), the statin should be discontinued. Other potential aetiologies should be considered before assuming that the elevated liver enzymes are due to the statin.

Take home messages
• Mild ALT elevation in isolation in asymptomatic statin users is not clinically relevant. In patients with mild ALT elevation due to statin therapy, there is likely to be a class effect of statins.
• Clinical apparent liver injury with statin use is very rare and likely to be a class effect of statins.
• Routine periodic monitoring of liver enzymes is not justified.
• Liver enzymes should be measured in the rare patient who develops symptoms suggestive of hepatotoxicity.

Haemorrhagic stroke
There is substantive evidence from RCTs that statin treatment reduces the risk of ischaemic stroke by 26% (99% CI 15–35%) per mmol/L reduction in LDL-C.119 While this benefit on ischaemic stroke is established, lower LDL-C levels have been associated with an increase in haemorrhagic stroke in the general population.120 The possibility that statins increase the risk of haemorrhagic stroke was suggested by a meta-analysis of over 8000 patients with a history of cerebrovascular events, which showed a higher risk of haemorrhagic stroke events (RR 1.73, 95% CI 1.19–2.50).119 These results were mainly driven by the SPARCL trial, which evaluated atorvastatin 80 mg/day in patients with a prior stroke or transient ischaemic attack and with LDL-C levels of 2.6–4.9 mmol/L (100–190 mg/dL).120 Atorvastatin reduced ischaemic stroke in SPARCL (218 events with atorvastatin vs. 274 with placebo), but produced a numerically higher number of haemorrhagic strokes (55 vs. 33). This event was more frequent in older individuals, men, or those with prior haemorrhagic stroke.121 A meta-analysis of eight RCTs (38 153 patients on statin therapy), showed a trend between attained LDL-C level and risk for haemorrhagic stroke, although the absolute number of haemorrhagic strokes was low.122

A subsequent meta-analysis including 248 391 patients, however, found no significant increased risk of intracerebral haemorrhage based on data from RCTs (RR 1.10, 95% CI 0.86–1.41), cohort studies (RR 0.94, 95% CI 0.81–1.10), and case–control studies (RR 0.60, 95% CI 0.41–0.88).123 A further meta-analysis of these patients found no association between the risk of intracerebral haemorrhage and the magnitude of LDL-C reduction.124 Moreover, even at very low attained LDL-C levels in FOURIER, there was no increase in the risk of haemorrhagic stroke.125

Take home messages
• Statin treatment reduces the risk of first or subsequent ischaemic strokes by 15–35% per mmol/L reduction in LDL-C.
• While SPARCL suggested a small increase in haemorrhagic stroke in subjects with prior stroke, this possible increased risk associated with LDL-C reduction has not been confirmed by analysis of a substantive evidence base of RCTs, cohort studies, and case–control studies.
• No alteration in the statin regimen in patients with a history of cerebrovascular disease is indicated.

Cataract
Age-related lens opacity (cataract) is the main cause of vision loss in the older population. Whether statin use exacerbates this risk has been a potential concern. Investigation of this question, however, has been hampered by methodological issues such as the lack of standardized definition of cataract as an outcome,126 as well as failure to account for the impact of statin adherence and the frequency of ophthalmological check-ups.

Observational data and limited preclinical studies suggested a possible link between cataract and statin use.127,128 A propensity score-matched analysis of a US administrative dataset of 46 249 subjects, including 13 262 statin users, showed that the risk of cataract was slightly higher (by 9%) with statin treatment.129 In addition, both the Heart Outcomes Prevention Evaluation (HOPE)-3 study and a retrospective nested case–control study showed an increase in risk for cataract surgery with statin use.129,130

On the other hand, evidence from RCTs provides reassurance on this question. In the Expanded Clinical Evaluation of Lovastatin (EXCEL) study in 8032 patients randomized to lovastatin (40 mg or 20 mg once or twice daily) or placebo, there were no significant differences in ocular opacities, visual acuity, or cataract extraction over a follow-up of 48 weeks.131 The Oxford Cholesterol Study Group trial in 539 patients randomized to simvastatin (40 mg or 20 mg daily) or placebo also showed no differences in visual outcomes or cataract grading after 18 months of treatment.132 Similarly, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study in 1873 patients with asymptomatic aortic stenosis and no history of diabetes, coronary heart disease, or other serious co-morbidities (average follow-up of 4.3 years) found that the risk of cataract was significantly lower with
the use of simvastatin and ezetimibe compared to placebo (hazard ratio 0.56, 95% CI 0.33–0.96). A subsequent meta-analysis of 313,200 patients in cohort trials ($n=6$, follow-up duration of up to 5 years), case–control studies ($n=6$, follow-up duration of up to 5 years), and RCTs ($n=5$, follow-up duration 0.9–5.4 years) did not show any association between statin use and the development of cataracts. Mechanistically, it has been suggested that the antioxidant and anti-inflammatory effects of statins could slow the development of cataracts, although further study is needed.

**Take home messages**
- Statin treatment is not associated with cataract development.
- No change in cardiovascular prevention strategies are indicated, even in patients with cataracts.

**Conclusion**
Public perception of the adverse effects of statins is often exaggerated, in part as a consequence of media reports. While statins generally have an acceptable safety profile, questions have been raised regarding possible unintended effects on glucose homeostasis, and cognitive, renal, and hepatic function, as well as the risk for haemorrhagic stroke or cataract. This Consensus Panel Statement therefore addressed these persistent uncertainties.

We conclude that statin treatment is remarkably safe. While there is a modest risk (about one new case per 1000 patients per year of exposure) of new onset DM with long-term statin treatment, this comes with the benefit of five new CVD events avoided. Patients with the metabolic syndrome or prediabetes are at higher risk of DM. In the absence of head-to-head studies, however, definitive statements as to whether any of the statins differ in their effect on glucose homeostasis are not possible. Statin use is not associated with adverse effects on cognitive function or clinically significant deterioration of renal function and does not increase the risk of cataract or haemorrhagic stroke in individuals without prior stroke, although the SPARCL data suggested statins may possibly increase the risk of haemorrhagic stroke in those with prior stroke. Clinical liver injury with statin therapy is very rare.

Finally, clinicians should be reassured by the long-term safety of statins, and the low risk of clinically relevant adverse effects, as discussed above. Importantly, and reinforcing recommendations from the recent European guidelines on CVD prevention and lipid management, the Panel emphasizes that the established cardiovascular benefits of statin therapy far outweigh the risk of any such adverse effects (Take home figure).

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