Adverse Effects of Statin Therapy: Perception versus the Evidence
Focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract

A Consensus Statement from the European Atherosclerosis Society Consensus Panel
Rationale
Why We Need This Statement

• Statins are recommended by guidelines as first-line treatments for reducing LDL-C, a key driver of atherosclerotic cardiovascular disease (ASCVD), as discussed in a previous EAS Consensus Statement.

• RCTs also show that statins are safe and generally well tolerated. However, most trials are:
  - Relatively short in duration
  - Tend to enrol a more homogeneous population than seen in routine practice.

**Why We Need This Statement**

- Perception by the general public of the long-term side effects of statins has also been influenced by media reportage.
- BUT are these side effects real – or a nocebo effect?

- Note: a nocebo effect is caused by negative expectations about the effects of treatment, due to information provided by clinicians and/or the media about possible side effects. This can lead to higher reporting rates than would otherwise be expected.

Why We Need This Statement

- This EAS Consensus Panel critically appraised the evidence for possible unintended effects of long-term statin therapy.
- This Statement accurately assessed the incidence of these effects so as to place perceptions of these side effects in their correct perspective.

Mach F et al. Eur Heart J 2018;
What are the Persistent Questions about Long-term Statin Safety?

- **Haemorrhagic stroke?**
  - No increase in risk, although SPARCL suggested a possible increase in risk with prior stroke

- **Cataract?**
  - No evidence for increased risk

- **Effects on cognition?**
  - No evidence that statins adversely affect cognitive function

- **Muscle symptoms**
  - Double-blind RCTs: 0.1-0.2%
  - Non-blinded observational studies: 7-29%

- **Dysglycaemia, new-onset diabetes**
  - RCTs: ~0.1 per year; individuals with metabolic syndrome or prediabetes are at greater risk

- **Proteinuria**
  - Low frequency of mild proteinuria: no evidence of clinically significant deterioration of renal function

- **Effects on liver**
  - Clinically relevant effects are very rare (~1 per 100,000)

Mach F et al. Eur Heart J 2018
The Evidence Reviewed:

- Review and analysis of literature search 200-2017
- Key questions:
  - What are the effects of statin treatment on glucose homeostasis?
  - What is the benefit vs. risk of statin therapy for new-onset diabetes mellitus, especially in patients with features of the metabolic syndrome?
  - What are the effects of statin treatment – and very low LDL-C levels – on cognitive function?
  - Does statin treatment affect renal or hepatic function?
  - Does statin treatment affect the risk for haemorrhagic stroke or cataract?
Statins and Glucose Homeostasis
### Statins and Glucose Homeostasis: Risk Vs. Benefit

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Risk of new-onset diabetes (per 1000 patients per year of exposure)</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sattar (2010)</td>
<td>1 new case</td>
<td>Prevents 5 new CVD events</td>
</tr>
<tr>
<td>13 RCTs in 91,140 patients without diabetes at baseline</td>
<td></td>
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<tr>
<td>Preiss (2011)</td>
<td>1 new case</td>
<td>Prevents 3.5 new CVD events</td>
</tr>
<tr>
<td>5 RCTs in 32,752 patients without diabetes at baseline, intensive statin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cederberg (2015)</td>
<td>10 new cases</td>
<td></td>
</tr>
<tr>
<td>8,749 men (2,142 on a statin) with features of metabolic syndrome</td>
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</table>

Statins and Glucose Homeostasis

What is the mechanism(s) for the increased risk of new-onset diabetes on statin treatment?

On-target effect? *HMGCR* gene variants associated with low LDL-C are also associated with higher blood glucose, insulin levels, body weight, waist circumference and BMI.

Class effect mediated by LDL? *PCSK9* and *NPC1L1* gene variants associated with low LDL-C were also associated with increased risk of diabetes ONLY in subjects with impaired glucose tolerance.

Off-target effects???

What is the Mechanism(s) of the Diabetogenicity of Statins?

Mach F et al. Eur Heart J 2018;
Statins and Glucose Homeostasis

Take Home Messages:

• Statins are associated with a modest risk of new-onset diabetes, about 1 new case per 1000 patients per year of exposure BUT also prevent 5 new cardiovascular events

• This risk may be higher in patients with features of the metabolic syndrome BUT needs to considered in context of the background conversion rate without statin treatment

• In most studies, new-onset diabetes was defined as an HbA1c >6.5 without symptoms BUT what is the relevance of this to long-term morbidity and mortality?

Mach F et al. Eur Heart J 2018;
Statins and Cognitive Function
# Statins and Cognitive Function: What is the Evidence?

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>FDA (2012); Data surveillance review</td>
<td>Labelling amendment to include cognitive side effects such as memory loss and confusion</td>
</tr>
<tr>
<td>Song (2013); 8 cohort studies, n=57,020 and 2,851 cases of dementia</td>
<td>Statin use was associated with a lower risk of dementia</td>
</tr>
<tr>
<td>Richardson (2013); 3 RCTs, 16 cohort, 4 case-control and 4 cross-sectional studies</td>
<td>No adverse effect of statins on cognition; rates of cognitive-related AEs similar to other cardiovascular medications</td>
</tr>
<tr>
<td>McGuinness (2014); Cochrane review 4 RCTs, 1154 with probable or possible dementia</td>
<td>Statin therapy does not delay deterioration of cognitive function in patients with dementia</td>
</tr>
<tr>
<td>Ott (2015); 25 RCTs (23 with cognitive testing), n=46,836</td>
<td>Statin therapy is not associated with cognitive impairment</td>
</tr>
</tbody>
</table>

...the incidence of neurocognitive adverse events did not increase at very low LDL-C levels (<0.78 mmol/L or <30 mg/dl)....

Giugliano RP et al. JAMA Cardiol 2017;2:547-55
Statins and Cognitive Function: FOURIER

No increase in the incidence of neurocognitive adverse events at LDL-C levels <0.50 mmol/L or <20 mg/dl....

...Low LDL-C levels were not associated with adverse effects on cognitive function as assessed prospectively over 19 months...

Statins and Cognitive Function

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.

Mach F et al. Eur Heart J 2018;
Statins and Renal Function
Statins: Effects on Major CVD events stratified by renal function

Statin therapy reduces CVD events in patients with CKD, especially those with mild kidney disease

Figure 2: Summary of the effects of statin therapy on major cardiovascular events stratified by kidney function. Only one trial and one subgroup (SHARP >60 and Rayner, 1996) were in chronic kidney disease (CKD) stage 2 with few endpoints (4 cardiovascular events and 105 patients), and we combined chronic kidney disease stage 3 and chronic kidney disease stage 2 into one subgroup.

Hou W et al. Eur Heart J 2013;34:1807-1817
Renal Clearance of Statins

• Most statins are metabolized by the liver and the renal clearance is minimal

• Hydrophilic statins, pravastatin and rosuvastatin, have significant clearance by the kidneys

• With the exception of patients on dialysis or with end-stage renal disease, no dose adjustment is recommended except for pravastatin and rosuvastatin

Mach F et al. Eur Heart J 2018;
## Statins and Renal Function

<table>
<thead>
<tr>
<th>Benefit</th>
<th>? Risk</th>
</tr>
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<tbody>
<tr>
<td>• Statin treatment reduces CVD events by 20% in patients with CKD</td>
<td>• Mild proteinuria, especially with intensive statin therapy BUT not associated with deterioration in function</td>
</tr>
<tr>
<td>• No benefit in dialysis patients</td>
<td>• Meta-analyses in CKD patients showed no increase in progression of CKD or acute renal events on statin therapy</td>
</tr>
</tbody>
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Statins and Renal Function

Take Home Messages:

- Statin treatment is not associated with clinically significant deterioration of renal function
- Dose reduction based on eGFR 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

Mach F et al. Eur Heart J 2018;
Statins and Hepatic Function
Background to Drug-Related Hepatotoxicity

• Drug-related hepatotoxicity is relatively uncommon
• True incidence is difficult to determine; spontaneously reported rates are likely to be an underestimate
• Difficult to detect in clinical trials
• Need to distinguish between injury and function
• Adults and females more sensitive
• Genetic susceptibility may be relevant

Mach F et al. Eur Heart J 2018;
## Statin-induced Elevation in Liver Enzymes

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective pooled analysis of 49 trials (n=14,236)</td>
<td><strong>Clinically relevant transaminase elevation with statin therapy is rare</strong></td>
</tr>
<tr>
<td>• 0.1%, 0.6%, and 0.2% of patients on atorvastatin 10 mg, 80 mg, or placebo had clinically relevant ALT elevation (≥3 x ULN on 2 occasions)</td>
<td></td>
</tr>
<tr>
<td>Network meta-analysis of 135 RCTs (n=246,955)</td>
<td></td>
</tr>
<tr>
<td>• Low frequency of clinically significant transaminase elevation with statin therapy</td>
<td></td>
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<tr>
<td>• Higher doses of statins were associated with higher likelihood of transaminase elevation</td>
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## Statin-Induced Liver Injury

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Conclusion</th>
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</table>
| UK General Practice Database (1997-2006)  
- Statin-induced liver injury is rare but higher with atorvastatin than simvastatin (0.09% versus 0.06%, hazard ratio 1.9, 95% CI 1.4-2.6, p<0.001)  
- Reporting rates were higher at higher doses | **Statin-induced liver injury is very rare** |
| FDA Adverse Drug Event Reporting System database  
- Reporting rates for severe statin-induced liver injury were very low (≤2 per million patient-years) | |
| Swedish Adverse Drug Reactions Advisory Committee (1998-2010)  
- Statin-induced liver injury reported for 1.2 per 100,000  
- Re-exposure to statin can produce the same response | |

Statins and Hepatic Function

Take home messages:

• Mild ALT elevation in isolation in asymptomatic statin users is not clinically relevant. In patients with mild ALT elevation due to steatosis or non-alcoholic fatty liver disease, statin therapy does not worsen liver disease.

• Clinically apparent liver injury with statin therapy 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.

Mach F et al. Eur Heart J 2018;
Statins and Risk for Haemorrhagic Stroke
Statins and Risk for Haemorrhagic Stroke

- CTT meta-analysis of statin trials: 14% increase in haemorrhagic stroke/mmol/L LDL-C reduction; BUT this was driven by the SPARCL data
- The risk for haemorrhagic stroke is outweighed by reduction in the risk of ischaemic stroke

<table>
<thead>
<tr>
<th>Events (% p.a.)</th>
<th>Statin/more</th>
<th>Control/less</th>
<th>RR (CI) per 1mmol/L reduction in LDL cholesterol</th>
<th>Adjusted heterogeneity test*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1122 (0.4)</td>
<td>1377 (0.5)</td>
<td>0.78 (0.71 – 0.87)</td>
<td>$\chi^2 = 1.42$ (p=0.23)</td>
</tr>
<tr>
<td>Women</td>
<td>418 (0.4)</td>
<td>485 (0.5)</td>
<td>0.87 (0.72 – 1.04)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1540 (0.4)</td>
<td>1862 (0.5)</td>
<td>0.80 (0.75 – 0.86)</td>
<td></td>
</tr>
<tr>
<td><strong>Haemorrhagic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>203 (0.1)</td>
<td>171 (0.1)</td>
<td>1.14 (0.87 – 1.49)</td>
<td>$\chi^2 = 0.01$ (p=0.94)</td>
</tr>
<tr>
<td>Women</td>
<td>83 (0.1)</td>
<td>71 (0.1)</td>
<td>1.16 (0.75 – 1.81)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>286 (0.1)</td>
<td>242 (0.1)</td>
<td>1.14 (0.96 – 1.36)</td>
<td></td>
</tr>
</tbody>
</table>
Statins and Risk for Haemorrhagic Stroke

Collaborative meta-analysis (n=248,391)
• No increase in risk of intracerebral haemorrhage in
  - RCTs (RR 1.10, 0.86-1.41),
  - Cohort studies (RR 0.94, CI 0.81-1.10)
  - Case-control studies (RR 0.60, 0.41-0.88)

Hackam DG et al. Circulation 2011;124:2233-2242
Statins and Risk for Haemorrhagic Stroke

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.
Statins and Risk for Cataract
Statins and Risk for Cataract

Take Home Messages:

• Statin treatment is not associated with cataract development.

• No change in cardiovascular prevention strategies are indicated, even in patients with cataracts.

Mach F et al. Eur Heart J 2018;
Statins: Highly Favourable Benefit vs. Risk Ratio

..’ the Panel emphasizes that the established cardiovascular benefits of statin therapy far outweigh the risk of any such adverse effects ‘

Mach F et al. Eur Heart J 2018;
European Atherosclerosis Society Consensus Panel:

European Heart Journal 2018;