CELL-PERMEABLE SUCCINATE BYPASSES STATIN-INDUCED MITOCHONDRIAL COMPLEX I INHIBITION IN HUMAN PLATELETS

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Disclosures

• I have no disclosures
What are statins?

• Statins are a group of lipid lowering medications known as HMG-CoA reductase inhibitors
• They are first line medication in the treatment of Hypercholesterolemia
Why are they so widely used?

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a bile acid sequestrant may be considered.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

- Atheromas regressed to similar degrees in patients with or without diabetes on high-intensity statin therapy.
- High-dose statin therapy is more effective than moderate- or low dose regimens to halt progression of atherosclerosis.
- Diabetic patients require fairly aggressive lipid therapy to get the same results as in nondiabetic patients.


Central Illustration: Statin-Associated Side Effects

Hydroxy-methyl-glutaryl CoA (HMG-CoA) reductase inhibitors (Statins)

- Mevalonate
- Farnesyl pyrophosphate (FFP)
- Cholesterol
- FOXO
- GGP
- Cellular cholesterol
- Atrogen-1
- Impaired insulin secretion
- Protein degradation, muscle atrophy, impaired mitochondrial function
- Coenzyme Q10
- Impaired mitochondrial function

↑HMG-CoA antibodies

Statin-induced necrotizing autoimmune myopathy (SINAM)
- Proximal muscle weakness
- Elevated creatine kinase (CK) levels
- Statin associated muscle symptoms (SAMS)
  - Myalgia and cramps
  - Clinical rhabdomyolysis
  - With/without increased CK elevations

Statin-associated symptoms (SAS)
- Diabetes mellitus
- Central nervous system complaints
- Other (elevated liver function, decreased renal function, tendon rupture, interstitial lung disease, depression, low testosterone, reduced risk of hemorrhagic stroke)

Statin-induced changes in mitochondrial function

- Disturbances in mitochondrial quantity and quality have been cited

- Decreased respiratory rates in intact platelets with unchanged respiratory capacity in rat platelets

- Reduction in NADH-linked respiration in human permeabilized platelets

- Decreased mitochondrial CII, CIII and CIV activity in muscle cells

Cerivastatin

- Was taken out of use due to a large number of cases of statin-induced rhabdomyolysis

- It has been shown to be toxic to mitochondria
Cell-permeable succinate prodrugs

• Increased Succinate-linked respiration in intact platelets with CI inhibition

• Attenuated lactate production

• Metabolomics confirms metabolism of delivered succinate
Aim of the study

• To assess the effects of two statins on platelet mitochondrial respiration in human platelets in the presence vs. the absence of NV118, a cell-permeable succinate prodrug
Materials and Methods

• High-resolution respirometry (OROBOROS - O2k)

• Peripheral blood platelets isolated from healthy volunteers

• Buffer MIR05

• SUIT protocols following acute incubation with cerivastatin
Dose-titration for the assessment of impairment of mitochondrial respiration

![Graph showing the effect of FCCP on mitochondrial respiration.

- **DMSO**
- **CERI**

Respiration (pmol O2 s^{-1} ml^{-1} 10^8 ptr^{-1})

Unpublished data
Dose-dependent impairment of mitochondrial respiration in permebilized platelets

Unpublished data
OMY effect on Cerivastatin-treated platelets vs. control

Unpublished data
FCCP max Cerivastatin - treated plateles vs. control

Unpublished data
Cerivastatin-induced dose-dependent decrease in respiration – Typical trace

**DMSO**

**Cerivastatin**
Atorvastatin-induced dose-dependent decrease in respiration – Typical trace

DMSO

Atorvastatin
Cell-permeable succinate bypassed Cerivastatin-induced mitochondrial CI inhibition and alleviated the respiration deficit - Typical trace
Cell-permeable succinate bypassed Atorvastatin-induced mitochondrial CI inhibition and alleviated the respiratory deficit - Typical trace

Control

Intervention
### CYP450 Drug Interactions With Statins

<table>
<thead>
<tr>
<th>CYP2C9</th>
<th>Statin Substrates</th>
<th>Common Inhibitors of CYP450 Pathway or Transporter System</th>
<th>Common Inducers of CYP450 Pathway or Transporter System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fluvastatin, rosuvastatin, pitavastatin</td>
<td>azole antifungals; amiodarone; gemfibrozil</td>
<td>Rifampicin, phenobarbital, phenytoin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP3A4</th>
<th>Statin Substrates</th>
<th>Common Inhibitors of CYP450 Pathway or Transporter System</th>
<th>Common Inducers of CYP450 Pathway or Transporter System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>atorvastatin, lovastatin, simvastatin</td>
<td>azole antifungals; amiodarone; azithromycin; erythromycin; clarithromycin; fluvoxamine; fluoxetine; sertraline; cyclosporine; tacrolimus; sirolimus; diltiazem; verapamil; protease inhibitors; grapefruit juice; posaconazole; ticagrelor, tricyclic antidepressants</td>
<td>Phenytoin, phenobarbital, barbiturates, rifampicin; omeprazole; carbamazepine</td>
</tr>
</tbody>
</table>

### Transporter Proteins And Statins

<table>
<thead>
<tr>
<th>OATP1B1</th>
<th>Statin Substrates</th>
<th>Common Inhibitors of CYP450 Pathway or Transporter System</th>
<th>None known at this time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin</td>
<td>carbamazepine, clarithromycin, cyclosporine, erythromycin, gemfibrozil, protease inhibitors, roxithromycin, rifampin, sildenafil, sacubitril, telithromycin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OATP1B3</th>
<th>Statin Substrates</th>
<th>Common Inhibitors of CYP450 Pathway or Transporter System</th>
<th>None known at this time</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>fluvastatin, pravastatin, rosuvastatin</td>
<td>clarithromycin, cyclosporine, erythromycin, rifampin, roxithromycin, rifampin, sacubitril, telithromycin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pgp-1</th>
<th>Statin Substrates</th>
<th>Common Inhibitors of CYP450 Pathway or Transporter System</th>
<th>Carbamazepine, phenytoin rifampin, St. John’s wort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>atorvastatin, lovastatin, pitavastatin, simvastatin</td>
<td>amiodarone, atorvastatin, azithromycin, captopril, carvedilol, cimetidine, clarithromycin, colchicine, conivaptan, cyclosporine, diltiazem, azole antifungal drugs, sertraline, tacrolimus, grapefruit juice</td>
<td>Car</td>
</tr>
</tbody>
</table>
Conclusions

• Acute administration of statins induced a dose-dependent impairment of mitochondrial respiration

• The cell-permeable succinate prodrug alleviated the mitochondrial respiratory defect

• The cell-permeable succinate prodrug bypassed the mitochondrial dysfunction induced by statins
Future direction

Further investigation of platelets isolated from patients chronically treated with statins in the presence vs the absence of the prodrug is envisaged.
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