Which of the following is not currently a recognized SLCO1B1 phenotype?

a) Low function
b) Normal function
c) Intermediate function
d) Ultra-rapid function
What is the predicted SLCO1B1 phenotype for a patient with a genotype of *1/*15?

a) Ultra-rapid metabolizer
b) Extensive metabolizer
c) Intermediate metabolizer
d) Poor metabolizer
A patient with a low function SLCO1B1 phenotype is at ____________ risk for developing myopathy if prescribed normal doses of simvastatin.

a) Low
b) Intermediate
c) High
d) Normal
Which of the following simvastatin dosing adjustments is correct for a patient with the \textit{SLCO1B1} \textit{*5/*15} genotype?

a) Consider an alternative statin agent  
b) Initiate simvastatin therapy at 20 mg/day  
c) Initiate simvastatin therapy at 40 mg/day  
d) Initiate simvastatin therapy at 80 mg/day
Objectives

- Upon completion of this competency, participants will be able to:
  - Recognize the different \textit{SLCO1B1} allele variants
  - Recognize the different \textit{SLCO1B1} phenotypes
  - Assign the correct phenotype based upon the allele variants
  - Make therapeutic recommendations for simvastatin dosing based on a patient's predicted \textit{SLCO1B1} phenotype
SLCO1B1 Pharmacogenetics
SLCO1B1

• SLCO1B1 stands for solute carrier organic anion transporter family member 1B1

• \textit{SLCO1B1} is a gene located on chromosome 12, that encodes for an organic anion transporter (SLCO1B1) that mediates the hepatic uptake of many endogenous compounds, such as bile acids, and several medicines including simvastatin.

• For these medications, dose adjustments or alternative therapies may be needed if there is impaired transporter function

Certain *SLCO1B1* alleles are characterized as wild-type (normal function) alleles

- These alleles will encode for SLCO1B1 with normal function

*SLCO1B1* normal function alleles include:

- *1a, *1b

• Certain *SLCO1B1* alleles are characterized as decreased function alleles
  – These alleles will encode for SLCO1B1 with intermediate or low function (most of them are carriers of the rs4149056 T<C polymorphism)

• *SLCO1B1* decreased function alleles include:
  – *5, *15, and *17

**SLCO1B1 Allele Variants**

- For certain *SLCO1B1* alleles, the function of the transporter is unknown and considered uncharacterized

- *SLCO1B1* alleles with unknown function include:

Assigning SLC01B1 Phenotypes
SLCO1B1 Phenotypes

- The assignment of SLCO1B1 phenotype is based on the two alleles of the patient (also called genotype or diplotype).
- There are three SLCO1B1 phenotypes:
  - Normal function
  - Intermediate function
  - Low function

The following table summarizes the most common allele variants and the likely SLCO1B1 function and associated phenotype.

<table>
<thead>
<tr>
<th>Functional Status</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>*1a, *1b</td>
</tr>
<tr>
<td>Decreased function</td>
<td>*5, *15, *17</td>
</tr>
<tr>
<td>Possible increased function</td>
<td>*14, *35</td>
</tr>
</tbody>
</table>

www.pharmgkb.org
SLCO1B1 Phenotypes

• Normal function
  — Have normal SLCO1B1 transport function
  — Homozygous wild-type/normal
  — The majority of patients
    • Approximately 71% of the population
  — Patient carrying two functional alleles
  — Diplotype examples:
    • *1a/*1a
    • *1a/*1b

**SLCO1B1 Phenotypes**

- **Intermediate function**
  - Have SLCO1B1 transport function that is in between the low and normal function patients
  - Heterozygous
  - Approximately 24% of the population
  - Patient carrying one normal function allele and one decreased function allele
  - Diplototype examples:
    - *1/*5
    - *1/*15

SLCO1B1 Phenotypes

- Low function
  - Have low SLCO1B1 transport function
  - Homozygous variant
  - Approximately 5% of the population
  - Patient carrying two decreased function alleles
  - Diplotype examples:
    - *5/*5
    - *5/*15

SLCO1B1 Phenotypes

• Indeterminate function
  — Expected phenotype cannot be determined based upon the \textit{SLCO1B1} genotype result
• For example, a patient may have two copies of an unknown function allele or one copy of an unknown function allele and one copy of a known function allele
  • *4/*7
  • *1a/*7
SLCO1B1 Phenotypes

Percentage of each phenotype in the population

- Normal Function: 71%
- Intermediate Function: 24%
- Low Function: 5%

* The exact percent of each phenotype group varies by ethnicity
Gene-Based Dosing Recommendations
Simvastatin
Simvastatin

- **HMG-CoA Reductase Inhibitor**
  - Inhibits cholesterol synthesis

- **Undergoes hepatic transport**
  - Substrate of SLCO1B1

- **Adverse effects**
  - Skeletal muscle toxicity is concentration- and dose-dependent (FDA black box warning for 80 mg dose)
    - Myalgia – pain
    - Myopathy – pain + muscle degradation
    - Rhabdomyolysis – severe muscle damage + acute kidney injury

Simvastatin

• Genetic variability in SLCO1B1 alters the plasma concentration of simvastatin

• A patient’s phenotype or function of the SLCO1B1 transporter is closely related to the risk of developing myopathy from normal doses of simvastatin

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Risk of Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Normal myopathy risk</td>
</tr>
<tr>
<td>Intermediate function</td>
<td>Intermediate myopathy risk</td>
</tr>
<tr>
<td>Low function</td>
<td>High myopathy risk</td>
</tr>
</tbody>
</table>
Simvastatin

- Lower doses or alternative medicines could be considered to reduce the risk of myopathy
- SLCO1B1’s effect on other statins is less compelling for the development of myopathy

<table>
<thead>
<tr>
<th>SLCO1B1 function</th>
<th>Dosing Recommendation for Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>No dosage change</td>
</tr>
<tr>
<td>Intermediate function</td>
<td>Consider starting with a lower dose of simvastatin</td>
</tr>
<tr>
<td></td>
<td>Consider an alternative statin agent</td>
</tr>
<tr>
<td>Low function</td>
<td>Consider an alternative statin agent</td>
</tr>
<tr>
<td></td>
<td>Consider monitoring creatine kinase (CK) levels routinely</td>
</tr>
</tbody>
</table>

Simvastatin

• These dosing recommendations and guidelines are specific to \textit{SLCO1B1} and simvastatin

• Although any medication that is a substrate for the \textit{SLCO1B1} transporter could be affected in the same manner, there currently are not enough data to provide dosing recommendations

• Other medications potentially affected include: Methotrexate, atorvastatin, mycophenolate mofetil, irinotecan, cytarabine
• For more information about SLCO1B1 and simvastatin dosing click here.

• For more information about pharmacogenetics visit the following website: www.pharmgkb.org

• For more pharmacogenetic service implementation resources visit the following website: www.stjude.org/pg4kds/implement
Which of the following is not currently a recognized SLCO1B1 phenotype?

a) Low function  
b) Normal function  
c) Intermediate function  
d) Ultra-rapid function  

Correct answer: d
What is the predicted SLCO1B1 phenotype for a patient with a genotype of *1/*15?

a) Ultra-rapid metabolizer
b) Extensive metabolizer
c) Intermediate metabolizer
d) Poor metabolizer

Correct answer: c
A patient with a low function SLCO1B1 phenotype is at ______________ risk for developing myopathy if prescribed normal doses of simvastatin.

a) Low
b) Intermediate
c) High
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Correct answer: c
Which of the following simvastatin dosing adjustments is correct for a patient with the \textit{SLCO1B1} *5/*15 genotype?

a) Consider an alternative statin agent
b) Initiate simvastatin therapy at 20 mg/day
c) Initiate simvastatin therapy at 40 mg/day
d) Initiate simvastatin therapy at 80 mg/day

Correct answer: a
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