SLCO1B1 Pharmacogenetic Competency

Updated on 6/2015

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Pre-test Question # 1

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

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

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Pre-test Question # 2

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

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Pre-test Question # 3

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

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Pre-test Question # 4

Which of the following simvastatin dosing adjustments is correct for a patient with the *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

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Objectives

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

SLCO1B1 Pharmacogenetics

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SLCO1B1

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

- ***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**

Ramsey LB, et al. *Clin Pharmacol Ther*. 2014;96(4):423-8.
Niemi N, et al. *Pharmacol Rev*. 2011;63:157-81.

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SLCO1B1 Allele Variants

- **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**

Ramsey LB, et al. *Clin Pharmacol Ther*. 2014;96(4):423-8.

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SLCO1B1 Allele Variants

- **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**

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SLCO1B1 Allele Variants

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

- ***SLCO1B1* alleles with unknown function include:**
  - ***4, *7, *8, *11, *12, *13, *16, *18, *19, *20, *21, *22, *24, *25, *26, *27, *28, *29, *30, *32, *33, *34, *36**

Ramsey LB, et al. *Clin Pharmacol Ther*. 2014;96(4):423-8.
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Assigning SLCO1B1 Phenotypes

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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**

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SLCO1B1 Phenotypes

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

Functional Status	Alleles
Normal function	*1a, *1b
Decreased function	*5, *15, *17
Possible decreased function	*2, *3, *6, *9, *10, *23, *31
Possible increased function	*14, *35
Unknown function	*4, *7, *8, *11, *12, *13, *16, *18, *19, *20, *21, *22, *24, *25, *26, *27, *28, *29, *30, *32, *33, *34, *36

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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***

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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**
  - **Diplotype examples:**
    - ***1/*5**
    - ***1/*15**

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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**

Ramsey LB, et al. *Clin Pharmacol Ther*. 2014;96(4):423-8.

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SLCO1B1 Phenotypes

- **Indeterminate function**
  - **Expected phenotype cannot be determined based upon the *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**

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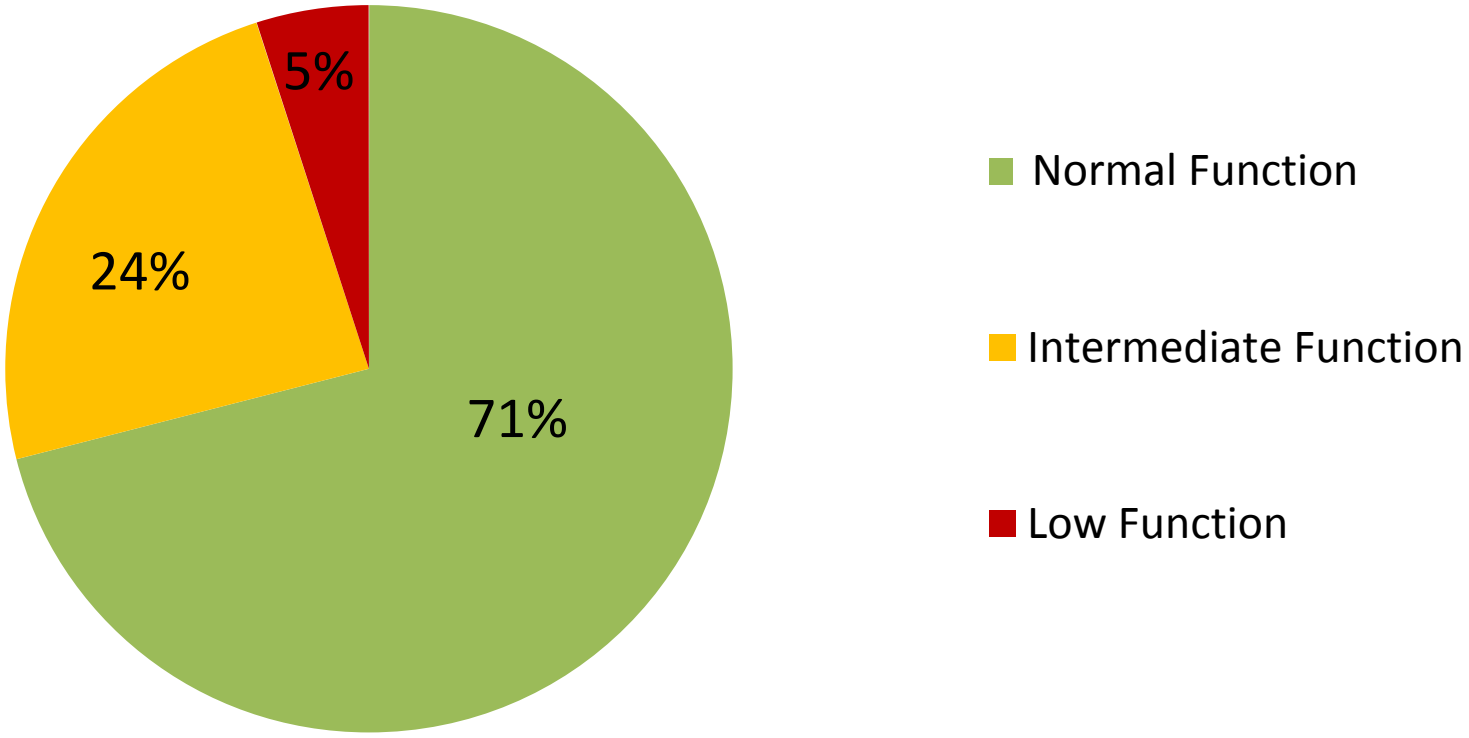
SLCO1B1 Phenotypes

Percentage of each phenotype in the population



*** The exact percent of each phenotype group varies by ethnicity**

Gene-Based Dosing Recommendations

Simvastatin

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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**

Niemi, M. *Clin Pharmacol Ther*. 2010;87:130-3.

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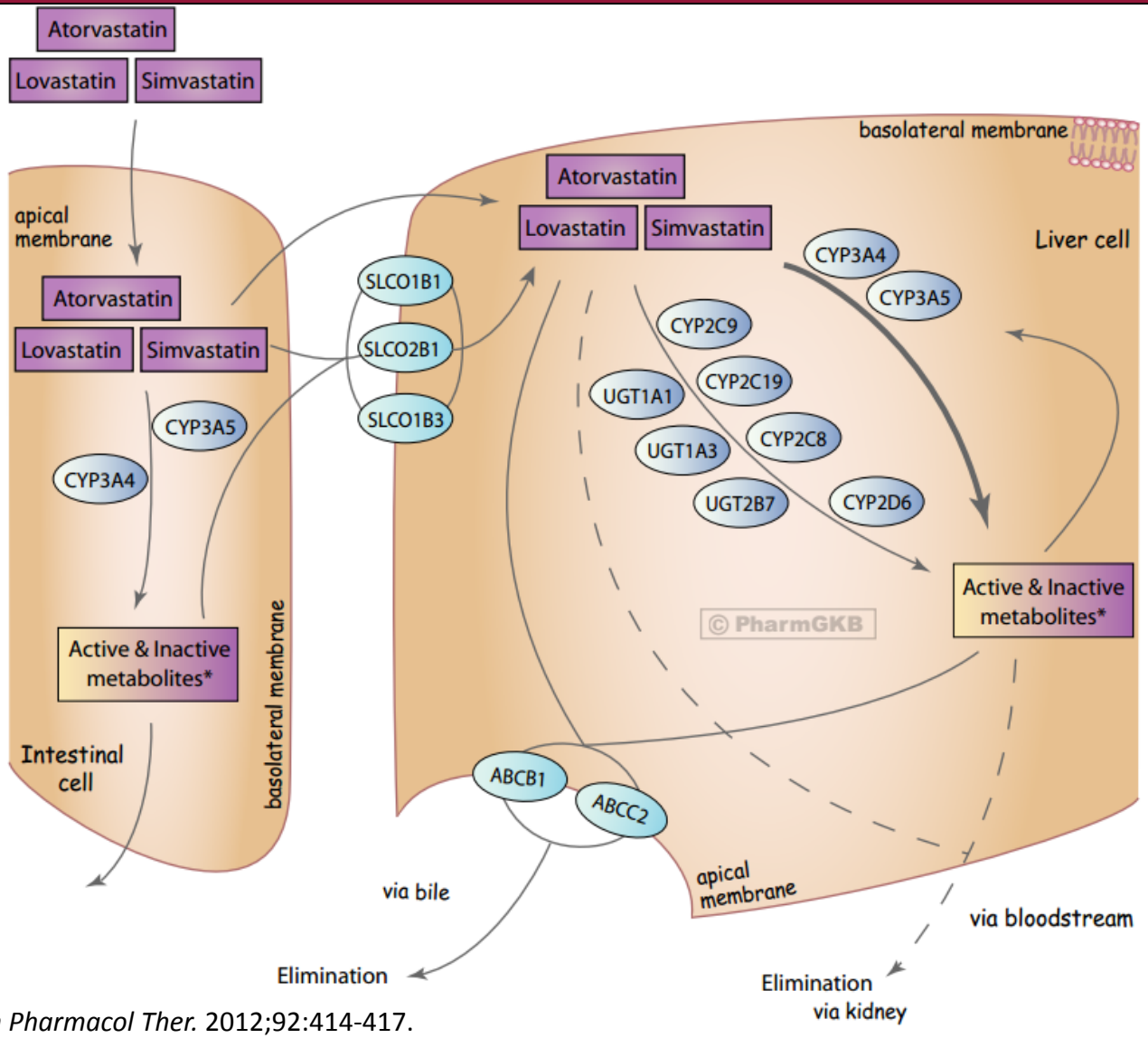
Simvastatin



Whirl-Carrillo M, et al. *Clin Pharmacol Ther.* 2012;92:414-417.

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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**

Phenotype	Risk of Myopathy
Normal function	Normal myopathy risk
Intermediate function	Intermediate myopathy risk
Low function	High myopathy risk

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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**

SLCO1B1 function	Dosing Recommendation for Simvastatin
Normal function	No dosage change
Intermediate function	Consider starting with a lower dose of simvastatin Consider an alternative statin agent
Low function	Consider an alternative statin agent Consider monitoring creatine kinase (CK) levels routinely

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Simvastatin

- **These dosing recommendations and guidelines are specific to *SLCO1B1* and simvastatin**
- **Although any medication that is a substrate for the *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

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For More Information…

- **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**

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Question # 1

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

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Correct answer: d

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Question # 2

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d) Poor metabolizer

Correct answer: c

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Question # 3

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