Dyslipidemia Update: Lipids, Genes, & New Drugs on the Scene

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Objectives

- Describe the pathophysiology of lipid disorders
- Evaluate recently approved and novel pipeline lipid therapies
- Apply pharmacogenomic principles to lipid management

Timeline of Recent Lipid Pharmacotherapy Changes

- Recent FDA Approvals for Dyslipidemia:
  - 2012: Juxtapid® (lomitapide) for Homozygous Familial Hypercholesterolemia (HoFH)
  - 2013: Kynamro® (mipomersen) for HoFH
  - 2014: Epanova® (2-D-carboxylic acid) for severe hypertriglyceridemia
  - 2015: Omtryg® (Ω-3 acid ethyl esters) for severe hypertriglyceridemia

- Recent Lipid-Related Pharmacogenomics Guideline Updates:
  - 2012: Clinical Pharmacogenomics Implementation Consortium (CPIC) Guideline for SLCO1B1 & Simvastatin
  - 2014: Clinical Pharmacogenomics Implementation Consortium (CPIC) Guideline for SLCO1B1 & Simvastatin - 2014 Update

Timeline of Recent Lipid Pharmacotherapy Changes

- Physiology of Lipid Transport & Metabolism
**Lipid Metabolism & Transport**

Liver:
- Acetyl Co-A
- Mevalonate
- Cholesterol \(\rightarrow\) Cholesterol Ester \(\rightarrow\) Apolipoproteins

Plasma:
- LDL \(\leftrightarrow\) IDL \(\leftrightarrow\) HDL

Lymphatic System:
- Chylomicrons

Intestines:
- Cholesterol

**Key Proteins Involved in Lipid Metabolism & Transport**

- **Proteins involved in:**
  - Lipid absorption
    - Microsomal triglyceride transport protein (MTP)
  - Lipid transport
    - Apolipoproteins (ApoA, ApoB, ApoC, ApoE)
      - combine with lipids to form lipoproteins which can be transported in the serum
    - Cholesterol ester transport protein (CETP)
      - transports cholesteryl esters from HDL to IDL and LDL
  - Lipid metabolism
    - Lipoprotein Lipase (LPL)
      - catalyzes breakdown of triglycerides
    - Hepatic uptake of lipids
      - LDL Receptor (LDLR)
      - Transports LDL into the liver or peripheral cells for storage or elimination
    - Proprotein convertase subtilisin/kexin type 9 (PCSK9)
      - Causes LDL receptor degradation

**Pathophysiology and Recently Approved Dyslipidemia Therapy**

**Familial Hypercholesterolemia (FH)**
- **Severe Hypertriglyceridemia (HTG)**
- **Secondary Hyperlipidemia (2˚ HLD)**

**Selected Dyslipidemias**

- **Familial Hypercholesterolemia (FH)**
  - Genetic basis:
    - LDL receptor
    - Apolipoprotein B
    - Proprotein Convertase Subtilisin Kexin 9 (PCSK9)
  - Homozygous FH
    - TC: 650-1000 mg/dL
    - Population prevalence: 1 in 1,000,000
    - Morbidity & mortality:
      - 20-fold increase in early-onset CHD risk (may occur as early as age 20)
      - 50% \(^2\) and 31% \(^2\) have a myocardial infarction before age 80
      - Xanthomas
  - Heterozygous FH
    - Population prevalence: 1 in 300-500
    - TC: 350-550 mg/dL

**Pathophysiology of FH**

Liver:
- Acetyl Co-A
- Mevalonate
- Cholesterol \(\rightarrow\) Cholesterol Ester \(\rightarrow\) Apolipoproteins

Plasma:
- LDL \(\leftrightarrow\) IDL \(\leftrightarrow\) HDL

Lymphatic System:
- Chylomicrons

Intestines:
- Cholesterol

Adapted From: Figure 2. The Pharmacogenomics Journal. 2006;(6):360–374.
Recently Approved Therapy Options for FH

• Lomitapide (Juxtapid®)
  – FDA Approved for HoFH in 2012
  – MOA: Microsomal Triglyceride Transfer Protein (MTP) inhibitor

Liver:

Plasma:

Lymphatic System:

Intestines:

and https://www.healthtap.com/topics/apolipoprotein-

Recently Approved Therapy Options for FH

• Mipomersen (Kynamro®)
  – FDA Approved for HoFH in 2013
  – MOA: antisense oligonucleotide

Liver:

Plasma:

Lymphatic System:

Intestines:

Copyright protected images available from: J Clin Endocrinol Metab. 2012;97(9):2969–2989.
and https://www.healthtap.com/topics/apolipoprotein-

Recently Approved Therapy Options for FH

• Mipomersen (Kynamro®)
  – Administration: weekly subcutaneous (SQ) injection
  – Efficacy:
    • ~25% LDL ↓ after 6 months of therapy vs. placebo
    • CV morbidity and mortality impact unknown
  – Safety:
    • BBW for hepatic steatosis/hepatotoxicity
      – 12% of patients had an elevation in ALT or AST ≥3xULN
    • Available for use only through REMs program
    • Long-term safety unknown
  – Cost of 28 day supply: $25,319.44

Mipomersen Package Label. Pricing data from Lexicomp.

Recently Approved Therapy Options for FH

• Alirocumab (Praluent®) & evolocumab (Repatha®)
  – FDA Approved for HeFH in 2015
  – MOA: Monoclonal Antibody (MoAb) binds to PCSK9, preventing it from binding to LDLR, & preventing LDLR from being degraded

Alirocumab Package Label. Pricing data from Lexicomp.
Recently Approved Therapy Options for FH

- **Alirocumab (Praluent®)** & evolocumab (Repatha®)

**Liver:**
- Acetyl Co-A
- Mevalonate
- Cholesterol → Cholesterol Ester → Apolipoproteins

**Intestines:**
- Triglycerides

**Plasma:**
- LDL
- IDL
- VLDL
- Apolipoproteins

**Lymphatic System:**
- LPL

**Selected Dyslipidemias**

- **Severe Hypertriglyceridemia**
  - Genetic basis for some forms of severe HTG:
    - Lipoprotein Lipase (LPL)
    - APOC2
    - APOA5
  - TG>750-1000 mg/dL
  - Population prevalence: 1 in 600
  - Morbidity & mortality:
    - Life-threatening, recurrent pancreatitis
    - Increase in CV risk, depending on type
    - Hepatosplenomegaly
    - Xanthomas

**Pathophysiology of Severe HTG**

- Acetyl Co-A
- Mevalonate
- Cholesterol → Cholesterol Ester → Apolipoproteins

**Plasma:**
- LDL
- IDL
- VLDL
- Apolipoproteins

**Lymphatic System:**
- LPL

**Recently Approved Therapy Options for FH**

- **Alirocumab (Praluent®)**
  - Administration: 75-150 mg SQ injection every other week
  - Efficacy:
    - ~55% LDL ↓ after 6 months of therapy vs. placebo
    - Long-term CV morbidity and mortality impact unknown
  - Safety:
    - Long-term safety unknown
    - Hepatic enzyme abnormalities occurred in <2.5% of patients
    - Injection site reactions (~7% of patients)
  - Cost of 28 day supply: $1,344.00

**Evolocumab (Repatha®)**

- Administration: 140 mg every 2 weeks or 420 mg once monthly SQ injection
- Efficacy:
  - ~50-65% LDL ↓ after 3 months of therapy vs. placebo
  - Long-term CV morbidity and mortality impact unknown
- Safety:
  - Long-term safety unknown
  - Hepatic enzyme abnormalities occurred in <2% of patients
  - Injection site reactions (~6% of patients)
- Cost of 28 day supply: $1,301.54-1,952.31

**Pathophysiology and Recently Approved Dyslipidemia Therapy**

Familial Hypercholesterolemia (FH)
Severe Hypertriglyceridemia (HTG)
Secondary Hyperlipidemia (2° HLD)

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J Clin Endocrinol Metab. 2012;97(9):2969-2989.`
Recently Approved Therapy Options for Severe HTG

- Icosapent ethyl (Vascepa®) – approved in 2012
- Ω-3 acid ethyl esters (Omtryg®) – approved in 2014
- Ω-3 carboxylic acid (Epanova®) – approved in 2014

Liver:

<table>
<thead>
<tr>
<th>Acetyl Co-A</th>
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Plasma:

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<thead>
<tr>
<th>LDL</th>
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Lymphatic System:

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Intestines:

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Selected Dyslipidemias

- Secondary Hyperlipidemia
  - No genetic basis
  - Elevated TC, LDL, TG
  - Population prevalence: 1 in 3 (elevated LDL)
  - Morbidity & mortality:
    - ≥ 2-4-fold increase in CHD risk vs. individuals without HLD

Pathophysiology of 2˚ HLD

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Intestines:

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Recently Approved Lipid Agents Data Summary

<table>
<thead>
<tr>
<th>Surrogate Marker Data in 1˚ Dyslipidemia</th>
<th>Surrogate Marker Data in 2˚ Dyslipidemia</th>
<th>CV Risk ↓ Data in 1˚ Dyslipidemia</th>
<th>CV Risk ↓ Data in 2˚ Dyslipidemia</th>
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</thead>
<tbody>
<tr>
<td>Lipid: (+)</td>
<td>Lipid: (+)</td>
<td>(+) or ADK or CVD</td>
<td>(+) or ADK or CVD</td>
</tr>
</tbody>
</table>

- Lomitapide (Juxtapid®)
- Mipomersen (Kynamro®)
- Icosapent ethyl (Vascepa®)
- Ω-3 acid ethyl esters (Omtryg®)
- Ω-3 carboxylic acid (Epanova®)
- Alirocumab (Prisitx®)
- Evolocumab (Repatha®)
Alirocumab (Praluent®) CV Outcomes Data

• **ODYSSEY LONG TERM Trial (n=2341)**
  – Population: (mean age = 60 with LDL ≥ 70 mg/dL)
    • HeFH (17.7%) or
    • CHD (68.9%) or
    • CHD risk equivalent (~41%)
  – Intervention: alirocumab 150 mg SQ every 2 weeks vs. placebo x 78 weeks
  – 1° Outcome: mean %Δ in LDL cholesterol from baseline
  – 2° Outcomes: ADEs & major CV events (post-hoc)


Alirocumab (Praluent®) CV Outcomes Data

• **ODYSSEY LONG TERM Trial Results**
  – Primary efficacy outcome (%Δ LDL at 24 weeks):
    • Alirocumab (n=1553): 61% LDL ↓ (52% ↓ @ 78 wks)
    • Placebo (n=788): 0.8% LDL ↑ (4% ↑ @ 78 wks)
  – Secondary safety outcomes:

    | Adverse Events | Alirocumab (%) | Placebo (%) | p-value |
    |---------------|----------------|-------------|---------|
    | Leading to drug discontinuation | 121 (7.9%) | 46 (5.9%) | 0.36 |
    | Injection site reaction | 91 (5.9%) | 10 (1.2%) | 0.20 |
    | ALT > 3x ULN | 27/1533 (1.8%) | 16/779 (2.1%) | 0.75 |
    | AST > 3x ULN | 25/1533 (1.4%) | 18/779 (2.3%) | 0.13 |
    | Myalgia | 84 (5.4%) | 23 (2.9%) | 0.006 |
    | Non-fatal MI | 14 (0.9%) | 18 (2.3%) | 0.01 |
    | Major CV event (post-hoc analysis) | 27 (1.7%) | 26 (3.3%) | 0.02 |


Alirocumab (Praluent®) CV Outcomes Data

• **ODYSSEY LONG TERM Trial Limitations**
  – Composite CV event endpoint in post-hoc analysis did not include all CV events:
    • CHF requiring hospitalization
    • Ischemia-driven coronary revascularization
    • When these events were included in the analysis, p=NS
  – Total # CV events was relatively small
  – ODYSSEY OUTCOMES Trial is planning to enroll 18,000 patients and scheduled to conclude ~2017


Evolocumab (Repatha®) CV Outcomes Data

• **OSLER-1 and OSLER-2 Trials (n=4465)**
  – Population: mean age= 58 with median LDL~120 mg/dL
    • HeFH (~10%) or
    • CHD (~20%) or
    • CV risk factor (~80%) or
    • Cerebrovascular Disease/PAD (~9%)
  – Intervention: evolocumab 140 mg SQ every 2 weeks or 420 mg monthly vs. standard therapy x 11.1 months
  – 1° Outcome: ADEs
  – 2° Outcomes: mean %Δ in LDL, non-HDL, & HDL cholesterol, TG, TC, ApoA1, ApoB, Lp(a), & CV events


<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Evolocumab (%)</th>
<th>Placebo (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>2060 (69.2%)</td>
<td>965 (64.8%)</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>222 (7.5%)</td>
<td>111 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Leading to drug discontinuation</td>
<td>71 (2.4%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>129 (4.3%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 (0.9%)</td>
<td>18 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt; 3x ULN</td>
<td>31 (1.0%)</td>
<td>18 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>CK &gt; 5xULN</td>
<td>17 (0.6%)</td>
<td>17 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>


Evolocumab (Repatha®) CV Outcomes Data

• **OSLER-1 and OSLER-2 Trial Results**
  – Primary outcome (ADEs):


Evolocumab (Repatha®) CV Outcomes Data

• **OSLER-1 and OSLER-2 Trial Results**
  – Secondary outcomes:
    • Lipid changes:
      – Mean LDL reduction: 73 mg/dL (61%, 95%CI: 59-63%, p<0.001)
      – Mean non-HDL reduction: 52% (p<0.001)
      – Mean HDL cholesterol increase: 7.0% (p<0.001)
      – Mean TG reduction: 32.8% (p<0.001)
      – Mean TC reduction: 36.1% (p<0.001)
      – Mean ApoA1 increase: 4.2% (p<0.001)
      – Mean ApoB reduction: 47.3% (p<0.001)
      – Mean lipoprotein(a) reduction: 25.5% (p<0.001)
  – CV events:
    – All CV event ↓: ARR = 1.23% (HR: 0.47, 95%CI: 0.28-0.78, p=0.003)
    – FOURIER CV outcomes study ongoing

Evolocumab (Repatha®) CV Outcomes Data

- OSLER-1 and OSLER-2 Trial Limitations
  - Relatively short duration (~1 year)
  - Study subjects had a wide range of CV risk at baseline
  - Study subjects were enrolled into OSLER-1 or OSLER-2 if they tolerated evolocumab in the 12 short-term (12 week) phase 2 trials
  - Open-label design
    - May have influenced CV and ADE reporting


New Data for Old Lipid Therapies

- Ezetimibe (Zetia®)
  - New 2° CV outcomes data published 2015 – IMPROVE-IT
  - MOA: Neimann-Pick C1-Like 1 Intestinal Cholesterol Transporter (NPC1L1)

Ezetimibe (Zetia®) 2° CV Outcomes Data

- IMPROVE-IT Trial (n=18,144)
  - Population: age>50 (mean age = 64) hospitalized for ACS in last 10 days with LDL > 50 mg/dL
    - Max LDL = 100 mg/dL if receiving lipid-lowering therapy
    - Max LDL = 125 mg/dL if not receiving lipid-lowering therapy
  - Intervention: simvastatin 40 mg daily + ezetimibe 10 mg daily vs. simvastatin 40 mg + placebo x 6 years
  - 1° Outcome: composite of: CV death, non-fatal MI, UA requiring hospitalization, coronary revascularization ≥30 days after randomization, or non-fatal CVA)


Ezetimibe (Zetia®) 2° CV Outcomes Data

- IMPROVE-IT Trial Results
  - Primary efficacy outcome (CV death or events):
    - Simvastatin + Ezetimibe (n=9,067): 32.7%
    - Simvastatin + Placebo (n=9,077): 34.7%
  - Secondary outcomes:

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>Simva + Ezetimibe</th>
<th>Simva + Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time-Weighted Average LDL</td>
<td>53.7 mg/dL</td>
<td>69.5 mg/dL</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>1233 (15.4%)</td>
<td>1233 (15.9%)</td>
<td>p = 0.78</td>
</tr>
<tr>
<td>Death from CV Causes</td>
<td>187 (2.3%)</td>
<td>188 (2.4%)</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>Death from CHD</td>
<td>449 (5.9%)</td>
<td>461 (5.8%)</td>
<td>p = 0.90</td>
</tr>
<tr>
<td>Any MI</td>
<td>977 (13.1%)</td>
<td>1118 (14.8%)</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>945 (12.8%)</td>
<td>1083 (14.4%)</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>33 (0.4%)</td>
<td>297 (0.4%)</td>
<td>p = 0.006</td>
</tr>
</tbody>
</table>

ARR = 2%
NNT = 50
95% CI: 0.89-0.99

Ezetimibe (Zetia®) 2° CV Outcomes Data

- IMPROVE-IT Trial Limitations
  - Dose titrations to high-intensity simvastatin (80 mg daily) were no longer allowed after June 2011 & 80 mg doses had to be reduced if duration <1 year
    - Alternate therapy could be substituted if LDL >100 mg/dL
  - Data from use of other statins would be informative

Future Lipid Therapy Targets

- Proteins enabling lipid metabolism & transport
  - Target: LDL receptors (LDLR)
  - Non-FDA Approved Therapies in Development: bococizumab (MoAb inhibitor of PCSK9)
  - Target: Cholesterol Ester Transfer Protein (CETP)
  - Non-FDA Approved Therapies in Development: anacetrapib, evacetrapib (CETP inhibitors)
Key Proteins Involved in Lipid Metabolism & Transport

Liver:
- Acetyl Co-A
- Fatty Acids
- Cholesterol
- Apolipoproteins
- LDL
- VLDL
- HDL

Plasma:
- LDL
- VLDL
- HDL
- Apolipoproteins

Lymphatic System:
- Cholesterol
- Triacylglycerides
- Apolipoproteins

Intestines:
- Cholesterol
- Triacylglycerides
- Apolipoproteins

Adapted from: Figure 2. The Pharmacogenomics Journal. 2006;(6):360–374.

Basic principles of statin pharmacogenomics & the 2014 CPIC Guideline Update

SLCO1B1 variant and simvastatin

Simvastatin Metabolism & Elimination

• SLCO1B1 (OATP1B1) is a hepatic transporter protein encoded by the gene SLCO1B1

Liver:
- CYP3A4
- CYP2C8
- Active & Inactive Simvastatin Metabolites

Plasma:
- Simvastatin
- Active & Inactive Simvastatin Metabolites

Intestines:
- Simvastatin
- Active & Inactive Simvastatin Metabolites

Adapted from: Figure 1. The Pharmacogenomics Journal. 2006;(6):360–374.

Genetics Review

• Human genome = 23 chromosome pairs
  - 20,000-25,000 genes comprised of 6 billion nucleotide base pairs
• Chromosomes
  - Comprised of hundreds of genes made up of hundreds of millions of base pairs
• Genes
  - Comprised of hundreds of thousands of base pairs that are transcribed into mRNA and translated into proteins

Genetics Review & Terminology

• DNA sequence encodes mRNA, which gets translated into amino acid sequences and assembled into proteins

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and http://publications.nigms.nih.gov/thenewgenetics/chapter1.html

PGx Terminology

• Genetic polymorphism
  - Allelic variant: alteration in the normal gene sequence
    • Usually results from Single Nucleotide Polymorphisms (SNPs)
  - Any genetic location at which at least two different sequences are found (“normal variation”), with each sequence present in at least 1% of the population
    • Mutations (<1% of population) vs. Polymorphisms (≥1%)
SLCO1B1 Variant

- **Gene: SLCO1B1**
  - The SLCO1B1 gene is located from base pairs 21,131,194-21,239,796 on chromosome 12
  - Encodes: SoLute Carrier Organic 1B1 transporter protein, which is also called the OATP1B1 or Organic Anion Transporting Polypeptide
    - Facilitates hepatic uptake of statins

SLCO1B1 Variant

- **Gene: SLCO1B1**
  - 5-20% of Individuals in the population have altered function of the SLCO1B1 (OATP1B1) protein
  - Altered function of SLCO1B1 is associated with increased area under the curve (AUC) of simvastatin
  - Individuals with a particular variant in the SLCO1B1 gene have demonstrated ~3-fold increase in myopathy risk with simvastatin therapy

SLCO1B1 Variant

- **Gene: SLCO1B1**
  - Genomic variation at the level of the DNA
    - In individuals with the variant allele:
      - A single nucleotide polymorphism occurs at the 21,176,615th base pair of the nucleotide sequence of Chromosome 12
  - Genomic variation at the level of the mRNA
    - Because this occurs at the 521st base pair after the start codon, this variant is sometimes also referred to as c.521T>C

SLCO1B1 Variant: c.521T>C

- Normal DNA sequence (5' to 3'): 5'...GTC...3'
- Normal DNA sequence (3' to 5'): 3'...CAC...5'
- Normal mRNA sequence: ...GUG...
- Amino acid (mRNA codon): ...Valine...
- Variant DNA sequence (5' to 3'): 5'...GCC...3'
- Variant DNA sequence (3' to 5'): 3'...CGC...5'
- Variant mRNA sequence: ...GCG...
- Amino acid (mRNA codon): ...Alanine...

SLCO1B1 Variant

- **Gene: SLCO1B1**
  - Genomic variation at the level of the amino acid sequence & protein
    - The altered mRNA sequence results in a variant codon in place of the normal 174th codon
      - Causes substitution of the amino acid Alanine in place of the normally occurring amino acid Valine in the amino acid sequence comprising the SLCO1B1 protein
      - At the protein level, the name for the variant is p.Val174Ala or p.V174A
      - This allelic variant is also referred to with the RefSNP ID of "rs4149056"

SLCO1B1 Variant

- **Gene: SLCO1B1**
  - Genotypes
    - TT = normal – normal myopathy risk
    - TC = variant (heterozygous) – increased myopathy risk
    - CC = variant (homozygous) – highest myopathy risk

### Nomenclature summary

<table>
<thead>
<tr>
<th>Gene</th>
<th>cDNA Variant</th>
<th>Protein Variant</th>
<th>Star Allele Name</th>
<th>Ref SNP ID</th>
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<tbody>
<tr>
<td>SLCO1B1</td>
<td>c.521T&gt;C</td>
<td>p.Val174Ala</td>
<td>*5</td>
<td>rs4149056</td>
</tr>
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### Genotypes

- TT = normal – normal myopathy risk
- TC = variant (heterozygous) – increased myopathy risk
- CC = variant (homozygous) – highest myopathy risk
SLCO1B1 Variant

• Clinical Pharmacogenomics Implementation Consortium Guideline (2012)

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Clinical Pharmacology and Therapeutics 2012;92(1):112-117.

SLCO1B1 Variant

• Clinical Pharmacogenomics Implementation Consortium Guideline Update (2014)

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