Triglyceride-rich Lipoproteins and Cardiovascular Disease: Importance and Management Update for Pharmacists

EDUCATIONAL OBJECTIVES
Upon completion of this activity, participants should be better able to:

1. Define triglyceride-rich lipoprotein types and explain the impact they have on the risk for cardiovascular disease;
2. Review the latest clinical trial data regarding genetic findings and the interaction between lipoproteins and inflammation on the development of atherosclerotic disease;
3. Identify currently recommended lifestyle therapy changes in the management of elevated triglycerides and triglyceride-rich lipoproteins;
4. Recognize the mechanism of action of triglyceride-lowering therapies, including the latest adjunct therapies to statin therapy;
5. Relate differences among the various EPA and DHA omega-3 fatty acid formulations, including dietary supplements on triglyceride-rich lipoproteins, atherosclerosis, and inflammation;
6. Discuss the most effective methods for counseling patients with hypertriglyceridemia about lifestyle modifications and treatment options; and
7. Develop competence on incorporating the medical therapy management (MTM) of triglyceride-rich lipoprotein into action plans.

Post-Test/Rationale

1. **Triglyceride-rich lipoproteins are thought to be associated with an increased risk for cardiovascular disease because of which of the following:**
   
   A. Inhibition of reverse cholesterol transport
   
   B. Accumulation of remodeled chylomicrons and very low-density lipoprotein cholesterol (VLDL-C) particles in atherosclerotic plaque***
   
   C. Up-regulation of low-density lipoprotein (LDL)-receptors
D. An increase in lipoprotein lipase enzyme activity in adipose tissue

**Correct Answer: B**

This remodeling produces remnant particles that are small enough to enter the vessel wall and accumulate in atherosclerotic plaque of both animals and humans. The remodeled chylomicrons and VLDL-C particles, referred to as remnants, have also been linked to the progression of coronary artery disease.

2. Genetic variants known to be associated with decreased triglyceride-rich lipoproteins include which one of the following:

A. Apolipoprotein (APO)-C3 loss of function***
B. APO-C5 mutations
C. APO-E5 mutations
D. Overexpression of lipoprotein lipase

**Correct Answer: A**

Lipoprotein lipase deficiency (Fredrickson Class I) is associated with genetic defects in APO-CII and APO-A5. Individuals with a genetic loss of function in APO-C3 have been shown to have a 35% to 40% reduction in plasma triglycerides and a 24% to 41% reduction in ischemic heart disease.

3. Restrictions on alcohol consumption by the American Heart Association (AHA) for patients with very high triglycerides indicate which of the following:

A. Limit of 2 alcoholic beverages per day
B. No specific restriction on alcohol other than to limit carbohydrate intake
C. Alcohol should be limited to 5% of the total daily caloric intake
D. Complete alcohol abstinence***

**Correct Answer: D**
Alcohol restriction is recommended by the National Lipid Association (NLA) as a routine strategy for to reduce triglyceride levels, while the AHA recommends complete alcohol abstinence along with reduced saturated fat intake for patients with very high triglyceride levels.

4. Which of the following drug classes should not be considered for the treatment of hypertriglyceridemia:

A. Statins
B. Ezetimibe
C. Bile acid sequestrants***
D. Niacin

Correct Answer: C

The primary effect of bile acid sequestrants is to reduce LDL-C, which is reduced in a dose-dependent manner, by approximately 15% to 30%. Bile acid sequestrants typically have no effect or may increase triglyceride levels.

5. According to a review in the National Library of Medicine Herbal Supplement Database of the dietary supplement omega-3 fatty acids, the average number of product servings determined to deliver a combined dose of eicosapentaenoic acid (EPA)-docosahexaenoic acid (DHA) of 3.4 grams/day was ________.

A. 4
B. 2
C. 8
D. 11***

Correct Answer: D
Another review of dietary fish oil supplements, which was identified in the National Library of Medicine Herbal Supplement Database, found that the combined content of EPA and DHA in 102 of these products ranged from as little as 30 mg per dose up to a maximum of 1452 mg per dose.\(^{36}\) This review found that a median of 11 supplement servings per day would be required to achieve a dose of 3.4 grams per day of omega-3 fatty acids.

6. Which of the following omega-3 fatty acids products has the least potential to increase LDL-C for patients with very high triglyceride levels:
   A. Omega-3-carboxylic acids
   B. Icosapent ethyl***
   C. Omega-3-acid ethyl esters (brand)
   D. Omega-3-acid ethyl esters (generic)
   **Correct Answer: B**

The combination EPA-DHA products also increase LDL-C (+26% and +45%), compared with a small reduction in LDL-C observed in those treated with icosapent ethyl (-5%). The clinical impact of the differential effect of these products on high-density lipoprotein cholesterol (HDL-C) and LDL-C is not known.

7. Which classes of lipid-modifying therapy have the greatest magnitude of effect in reducing plasma triglycerides?
   A. Niacin, statins, and ezetimibe
   B. Niacin, omega-3 fatty acids, and fibrates***
   C. Niacin, bile acid sequestrants, and ezetimibe
D. Statins, fibrates, and omega-3 fatty acids

Correct Answer: B

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Change in Plasma Triglyceride Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>20% to 50%</td>
</tr>
<tr>
<td>Statins</td>
<td>7% to 30%</td>
</tr>
<tr>
<td>Immediate-release niacin</td>
<td>20% to 50%</td>
</tr>
<tr>
<td>Extended-release statin</td>
<td>10% to 30%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5% to 10%</td>
</tr>
<tr>
<td>Omega-3 Fatty Acids</td>
<td>20% to 50%</td>
</tr>
</tbody>
</table>

8. When counselling patients with hypertriglyceridemia, this population should be advised that the most common side effects of omega-3 fatty acids include which of the following:

A. Myalgia
B. Hypertransaminasemia
C. Gastrointestinal***
D. Facial flushing

Correct Answer: C

The most common side effects from treatment with omega-3 fatty acids include eructation, nausea, diarrhea, and other mild gastrointestinal disturbances. Studies with prescription omega-3 fatty acids products have found no adverse effect on liver function.
9. The addition of which of the following non-statin therapies has been demonstrated to further reduce adverse cardiovascular risk for patients on statin therapy:
A. Ezetimibe, omega-3 fatty acids***
B. Niacin, ezetimibe
C. Ezetimibe, fibrates
D. Fibrates, omega-3 fatty acids

Correct Answer: A

Studies with fenofibrate alone or in combination with a statin have failed to demonstrate a reduction in adverse outcomes. The addition of niacin to statin therapy has also not resulted in a reduction in cardiovascular events. The use of the omega-3 fatty acids has been shown to reduce adverse cardiovascular events for patients taking statins for secondary prevention. Ezetimibe is one of the only non-statins that, when added to statin therapy, has demonstrated a reduction in cardiovascular risk beyond statin monotherapy.

10. When prescription omega-3 fatty acids products are used to treat patients with high triglyceride levels (200 to 500 mg/dL), the average range for the decrease of plasma triglycerides is
A. 40% – 50%
B. 35% – 40%
C. 17% – 28%***
D. 5% – 10%

Correct Answer: C
The magnitude of the reduction in triglycerides is somewhat more consistent in this patient population, with a range from 17% to 28%.

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Omega-3-carboxylic acids</th>
<th>Omega-3-acid ethyl esters</th>
<th>Icosapent ethyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>-5.9</td>
<td>-20.6</td>
<td>-3.5</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-0.9</td>
<td>-6.9</td>
<td>-1.5</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+2.2</td>
<td>+3.3</td>
<td>-1.1</td>
</tr>
<tr>
<td>TC</td>
<td>+0.5</td>
<td>-3.8</td>
<td>-1.5</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>-5.9</td>
<td>-21.5</td>
<td>-4.8</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+1.1</td>
<td>+1.3</td>
<td>-1.9</td>
</tr>
<tr>
<td>APO-B</td>
<td>+0.3</td>
<td>-2.1</td>
<td>-1.2</td>
</tr>
</tbody>
</table>